(Second Edition)

HEMATOLOGY

By

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CHARLES C THOMAS PUBLISHER

Springfield Illinois USA

CHARLES C THOMAS PUBLISHER
BANNERSTONE HOUSE
301–327 East Lawrence Avenue Springfield Illinois U S A

Published simultaneously in the British Commonwealth of Nations by
BLACKWELL SCIENTIFIC PUBLICATIONS LTD OXFORD ENGLAND

Published simultaneously in Canada by
THE RYERSON PRESS TORONTO

First Edition 1948
Second Edition 1955

Library of Congress Catalog Card Number 54 10800

Printed in the United States of America

Dedicated

to the late

HENRY A CHRISTIAN

My chief for the first ten years of my medical experience who formerly served as Hersey Professor of the Theory and Practice of Physics Harvard University Clinical Professor of Medicine Tufts College Medical School Physician in Chief Peter Bent Brigham Hospital Visiting Physician Beth Israel Hospital Boston

In grateful acknowledgment of my profound indebtedness to him for his example counsel guidance and the opportunities which he made available to me

PREFACE TO SECOND EDITION

WITH THE revision of the First Edition of this book an opportunity is afforded to include the significant advances which have been made in hematology in the past five years Among the more important ones have been the isolation and identification of vitamin B_{12} now recognized as the extrinsic factor of Castle and the active principle of liver effective in the treatment of pernicious anemia the introduction of the folic acid antagonists triethylene melamine and nitrogen mustards ACTH and cortisone in the treatment of leukemia and allied conditions the therapeutic effectiveness of ACTH and cortisone in idiopathic thrombocytopenic purpura and acquired hemolytic anemia a clarification of the indications for splenectomy and a widening of our knowledge concerning drugs as etiologic agents in hematologic disorders especially aplastic anemia and agranulocytosis

Every page of the book has been carefully scrutinized and many revisions inserted along with suitable deletions The space dealing with the historical aspects of hematologic disorders although extensive has not been curtailed as comments by reviewers indicate that in general it has received a favorable reception

The science of hematology is not static but is as fast moving as any other division of medical knowledge A textbook such as this therefore cannot be expected to be entirely complete even if it were revised every few months An effort has been made however to include the important facts concerning each hematologic disorder which appear to have been established beyond the question of a doubt and to attempt an evaluation of the significant new advances in this field

To Dr Frank H Bethell Professor of Internal Medicine and Assistant Director of the Thomas Henry Simpson Memorial Institute for Medical Research University of Michigan and to Dr Muriel Meyers Associate Professor of Internal Medicine and Research Assistant in the Institute I am especially indebted for their generous aid counsel and guidance which have been invaluable to me To Miss Mary A Kinney my secretary I am especially grateful for her constant assistance and valuable direction in the preparation of the revised manuscript

I am greatly appreciative of the assistance and encouragement given to me in the preparation of this Second Edition by my publisher Mr Charles C Thomas and his staff

CYRUS C STURGIS

Ann Arbor Michigan

PREFACE TO FIRST EDITION

One of the most appropriate utterances that has come to my attention concerning the writing of a textbook of medicine is as follows "Everyone who writes a textbook on any branch of experimental science must set down as many wrong statements as right he cannot carry out most experiments himself he must rely on the testimony of others and often take probability for truth Thus a compendium is a monument of the time when the facts were collected and it must be renewed and rewritten again and again But while fresh discoveries are accepted and a few chapters improved others perpetrate misleading experiments and erroneous deductions" (From the *Theory of Colour* by Goethe)

This remarkably true statement by a master poet and philosopher deserves the careful consideration of all prospective authors of medical texts *This is because the medical sciences are now moving forward so* rapidly that the writing of a monograph on any one phase of the practice of medicine necessitates the constant evaluation and sifting of an almost endless amount of material which is appearing at an increasing tempo in the current medical literature One must apply himself diligently to the task of sorting the good from the bad differentiating carefully between matters of ephemeral importance and those of permanent value *and of assigning the proper amount of space to the various aspects of* different disease syndromes

The late Harvey Cushing once told me that no one should become the author of a medical book until after he had attained the age of 50 years This remark has remained in my memory although an appreciation of its significance was not aroused until more recent years While many admirable medical books have been written by young authors nevertheless an increasing age has some advantage because it at least provides a longer period of time to accumulate experience and hence formulate more mature and permanent judgments *It is the utilization of the faculty of critical discrimination based upon an extensive well balanced* general clinical experience that enables one to avoid to a certain extent the pitfalls described so adequately by Goethe

It seems appropriate in the preface of a book dealing with this subject to comment briefly upon hematology as a specialty There has been a regrettable tendency since the rapid development of the laboratory aspect of medicine to place unwarranted reliance upon technical tests and to minimize the importance of the information derived from the history and physical examination of the patient Some hematologists for

example have been too content to limit their examination to a blood film and then attempt to express a definitive opinion in regard to the patient's entire clinical picture. Despite the warnings of experienced clinicians this practice continues and undoubtedly favors error and the improper management of the patient.

Furthermore, in hematology as in cardiology or gastroenterology, or any other branch of medicine, the patient has not infrequently suffered from the narrow efficiency of specialism. This means that a physician may be preeminent in his own *chosen field but conspicuously deficient* or disinterested or both in the other aspects of medicine. In my opinion the ideal situation in hematology or any other branch of internal medicine is the practice of a specialty by a physician who has an excellent background and training in internal medicine but a special interest in some one branch of it. Such a physician is not likely to be misled by a laboratory examination, for his clinical balance provides him with a method whereby all which has a bearing on the patient's condition may be properly evaluated. All mature clinicians agree that the information derived from the labo*ratory should only be employed in* a confirmatory manner, for there are few diseases which can be recognized from tests of this nature alone.

On the other hand the availability of laboratory tests which are done accurately by carefully trained individuals and the correlation of these data with that derived from all other sources constitutes the ideal method of practicing our profession. Often such a broad method of accumulating diagnostic information is the crux of the difference between the practice of good and bad medicine.

Perhaps some explanation should be offered for the prominence which has been given in this publication to the historical aspects of hematology. There have been two reasons for this. In the first place this phase of hematology has been largely ignored in many previous monographs and textbooks, and it is my opinion that its inherent interest alone merits more than cursory attention. Second, and probably of greater importance, is my firm conviction that a scholarly knowledge of any branch of medicine can only be based upon a clear understanding of the principal advances and their sequential development which has lead to our present total fund of information in any particular field. While it is possible, of course, to acquire a sufficient number of current facts relating to any disease which will serve for many practical purposes, a true and profound insight into any complex subject can only be based upon a historical study dealing with the evolution of each forward step. Hence it should be emphasized that any scientific matter must be studied historically in order to acquire a proper appreciation of the contemporary knowledge relating to it and about which we may speak so glibly today.

In hematology, as in other branches of medicine, progress was not continuous but halting, that is, with the invention of some instrument

such as the microscope the hemocytometer a new method of staining or under the guiding mind of such a genius as Virchow Hayem Ehrlich or some other equally great hematologist new and important information was acquired with amazing rapidity Periodically with the diversion of scientific studies elsewhere interest in hematology has waned and in some instances it was maintained for a period of years by only a slender thread Although fragile it sufficed to sustain the spark of interest until some unpredictable influence fanned the flame anew

The story of the accumulation of knowledge in any special field of medicine is fascinating for it is one of persevering interest false starts with the pursuit of some facts into a cul de sac of disappointment which necessitated a retreat and a new beginning As so frequently happens the investigator to whom the credit is given may have been preceded by years by some unknown but brilliant scientific semi recluse who made but did not give the world his discoveries Many historical surveys show that the path leading to scientific discoveries is not always pleasant for it may be interwoven with bitter personal and international controversies false claims and counter claims and the lack of recognition either with financial reward or scientific acclaim But finally there is the consoling fact that ultimately justice will always prevail and the proper credit and recognition be given This is alas sometimes delayed for years or even centuries

Special attention has been given in this publication to the preparation of a carefully selected bibliography This in my opinion adds greatly to the reference value of any textbook and hence the *extensive list of items has been chosen with great care* As my colleagues and I at the Simpson Memorial Institute of The University of Michigan for a number of years wrote the review on hematology for the *Archives of Internal Medicine* an opportunity was afforded to inspect a wide variety of articles some of which otherwise would have been overlooked Even with great care it is always regrettable that a number of important presentations are unintentionally omitted For such oversights I wish to extend my apologies

Unusual care has been taken to make the bibliographical references accurate and hence not perpetuate errors which have been known to continue through several generations In each instance with exceedingly rare exceptions the original texts have been consulted and the reference verified For this opportunity I wish to extend my warm thanks to Miss Sue Biethan former Medical Librarian of the University of Michigan whose assistance and cooperation cannot be over estimated I desire also to express my appreciation to the Staffs of the Surgeon General's Library the John Crerar Library the Library of the American Medical Association and the editors of many medical publications who have given permission to reproduce charts tables and other material from various

periodicals Acknowledgment of this in each individual case is made in the text

It is with pleasure that I acknowledge my indebtedness and gratitude to my secretaries Mary Kinney and Marguerite Madden Laetz whose assistance cooperation and perseverance has been far above that required in the line of duty Without their constant aid and encouragement this book would never have been completed

My publisher Mr Charles C Thomas and his son Mr Payne Thomas have been most helpful in making many suggestions and in giving their most careful and meticulous attention to the numerous details concerning the publishing of this book To them I wish to extend my most sincere expression of gratitude In conclusion, I wish to state that I am greatly indebted to my friend of many years standing Dr Lawrence Reynolds Editor of *The American Journal of Roentgenology and Radium Therapy* who was responsible for directing my attention toward the publication of this work on hematology Had he not made the suggestion at precisely the proper moment it is doubtful that my labors would have ever turned in this direction

CYRUS C STURGIS

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HEMATOLOGY

CHAPTER I

CLASSIFICATION AND GENERAL REMARKS CONCERNING THE ANEMIAS

Definition.—An anemia may be defined as a diminished concentration of hemoglobin or erythrocytes or both in the circulating blood below the normal standards for sex and age. The lower limit of normal for adult males is given by Albritton (*1*) as 4.6 million red blood cells per cubic millimeter and a hemoglobin of 14.0 grams per 100 cc. of blood. For adult females these values are stated as 4.2 million red blood cells per cubic millimeter and a hemoglobin concentration of 11.5 grams per 100 cc. of blood. The standards given by Wintrobe (2) are a red blood cell count of 4.6 millions per cubic millimeter for adult males with a hemoglobin concentration of 14.0 grams per 100 cc. of blood and for adult women a minimum red blood cell count of 4.2 millions per cubic millimeter and a hemoglobin of 12.0 grams per 100 cc. of blood. From my own experience in the northern part of the United States *I would place the lower limit of normal for hemoglobin at 12.2 grams (78 per cent per 100 cc. of blood) for women and 13.4 grams (86 per cent) for men. The minimum red blood cell count I have considered to be 4.13 millions per cubic millimeter for women and 4.7 millions for men.*

Strictly speaking, a true anemia means an actual decrease in the total amount of hemoglobin or number of red blood cells in the entire body which involves a consideration of the blood volume. For instance, there is the so-called physiological anemia of pregnancy in which the red blood cell count and hemoglobin are decreased as determined by the usual methods. This is not a true anemia, however, but a diminished concentration due to the fact that the plasma volume is increased. Under these circumstances the total number of red blood cells and grams of hemoglobin in the entire body are not less than normal but are merely present in a decreased concentration. The situation is reversed in acute hemorrhage, for although there may be considerable loss of hemoglobin and erythrocytes, their values in the circulating blood immediately after the bleeding are normal. This is because the blood volume is decreased and as a result there may be no change in the concentration of the erythrocytes in the circulating blood although their actual total number in the body may be decreased.

Symptoms and Signs of Anemia.—There are certain symptoms common to all anemias regardless of the cause which becomes apparent when the

be normal Such a mechanism while efficient would place an undue load on the circulatory system if it were the only means of overcoming the tissue anoxia Fortunately the body has another compensatory mechanism which is of assistance This is because when anoxia is present more oxygen is removed from the arterial blood as it flows through the tissues Normally about 30 per cent of the oxygen is released but in the severest anemias as much as 80 to 90 per cent is removed Hence an increased cardiac output and a greater removal of the available arterial oxygen provides in part at least for the deficiency of the oxygen carrying power of the blood due to the reduction in hemoglobin

The chief symptoms arising from the cardiovascular system in patients with anemia are dyspnea and palpitation on exertion There is usually no dyspnea at rest nor is there orthopnea or paroxysmal dyspnea Palpitation also appears usually on exertion only and is due to the tachycardia and increased force of the cardiac impulse On physical examination patients with anemia often show a wide pulse pressure a borderline or slightly enlarged heart a blowing systolic murmur at the apex and very rarely a diastolic murmur Although *electrocardiographic* changes occur in about 25 per cent of the patients with chronic anemia they are usually of minor degree and of no clinical importance They are probably due to the anoxia as in most instances they disappear when the blood returns to normal unless there is some other associated change such as that due to arteriosclerosis The symptoms of *angina pectoris* never result from the anemia alone in my experience but always are associated with some other unrelated alteration in the coronary vessels usually due to arteriosclerosis The anemia however plays a contributing role as the underlying pathology may not cause angina pectoris when the blood returns to normal The anemia may also contribute to the development of *intermittent claudication* and *congestive failure*

It is emphasized by Blumgart and Altschule (6) that two other changes not ordinarily considered are of importance in causing cardio-respiratory symptoms in patients with an anemia They are first that the *vital capacity* is often reduced due to loss of elasticity and expandability which contributes to the shortness of breath and second that with an anemia there is also an impairment in the *carbon dioxide carrying power* of the blood It is thought however that the decreased availability of carbon dioxide as a buffer is compensated for by the overventilation which renders the blood more alkaline With a reduction in the hemoglobin there is a parallel decrease in the carbonic anhydrase which leads to a decreased ability of the hemoglobin to absorb carbon dioxide from the tissues and to release it in the lungs

All patients with an anemia of any severity have symptoms referable to the *nervous system* These are inability to concentrate irritability,

hemoglobin falls to the level of approximately 11 0 grams per 100 cc (70 per cent) The main clinical evidences of an anemia are ease of fatigue weakness and the cardio respiratory symptoms and signs which are directly referable to the anoxia of the tissues resulting from the impaired oxygen carrying capacity of the blood due to its decreased hemoglobin content The manifestations are for the most part, directly proportional to the level of the hemoglobin

TABLE I

NORMAL VALUES OF RED BLOOD CELL COUNT HEMOGLOBIN CONCENTRATIONS HEMATOCRIT READINGS AND VARIOUS CORPUSCULAR VALUES FROM BIRTH TO MATURITY

Age	Red Blood Cell Count (Millions per C Mm)	Hemoglobin (Gm per 100 Cc)	Vol Packed R B C (Cc per 100 Cc) Hematocrit	Corpuscular Values M C V (C μ)	M C H C (Per Cent)	M C H
At Birth	5 7 Range 4 8–7 1	21 5 Range 18–27	56 6	106	38	38
End 4th Week	4 7 Range 3 9–5 9	15 6 Range 12–21 8	44 6	91	35	33
End 12th Mo	4 6 Range 4 0–5 5	11 6 Range 9–14 6	35 2	77	33	25
End 12th Year	4 8 Range 3 8–5 4	13 4 Range 11–16 5	39 6	81	33 8	28
Adult Male	5 4 Range 4 6–6 2	15 8 Range 14–18	47	87	33 5	29
Adult Female	4 8 Range 4 2–5 4	13 9 Range 11 5–16 0	42	87	33 5	29

(Based on data presented by Albritton (1))

The *cardio respiratory* symptoms and signs are usually encountered in patients with an anemia when the hemoglobin level of the circulating blood falls to 11 0 grams per 100 cc or lower Comprehensive studies on the cardiovascular system in patients with anemia have been reported by Ellis and Faulkner (3), by Wintrobe (4) by Hunter (5) and by Blumgart and Altschule (6) According to Blumgart and Altschule (6) when the oxygen carrying capacity of the blood is lowered as it always is when an anemia is present an anoxia of the tissues will result unless one or both of two mechanisms are brought into play effectively One is an increased cardiac output which will augment the blood being delivered to the tissues If the hemoglobin is reduced one half but the rate of blood flow is doubled the amount of oxygen reaching the tissues will

be normal. Such a mechanism while efficient would place an undue load on the circulatory system if it were the only means of overcoming the tissue anoxia. Fortunately the body has another compensatory mechanism which is of assistance. This is because when anoxia is present more oxygen is removed from the arterial blood as it flows through the tissues. Normally about 30 per cent of the oxygen is released but in the severest anemias as much as 80 to 90 per cent is removed. Hence an increased cardiac output and a greater removal of the available arterial oxygen provides in part at least for the deficiency of the oxygen carrying power of the blood due to the reduction in hemoglobin.

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All patients with an anemia of any severity have symptoms referable to the *nervous system*. These are inability to concentrate, irritability,

faintness dizziness, malaise and mild headaches It is likely also that the chief symptoms of an anemia the ease of fatigue and weakness are in part due to anoxia of the nervous system as well as to the muscular tissues Studies on *blood flow through the brain* by Himwich and Fazekas (7) indicate that although it is abnormally rapid it is thought that the brain tissue oxygen tension is low and that this may account for the mental symptoms of patients with anemia It is known that patients with severe anemia may have a decreased ability to *concentrate urine* and also have a polyuria and an albuminuria The total blood flow through the kidneys may be reduced by a third or half as shown by Bradley and Bradley (8) As the amount of plasma for filtration is not reduced however one would not expect that nitrogen retention would be present as it rarely is There is some evidence that tubular function is impaired and that salt retention may be present *Gastro intestinal* symptoms of which anorexia is the most important are present in almost all patients with anemia and account mainly for the loss of body weight In some instances there may be mild nausea and flatulence The exact cause of the gastric symptoms is not known but it is usually attributed to the anoxia and possibly the reduction in gastric acidity which commonly results from any type of severe anemia Patients with a hemoglobin of 10 grams per 100 cc commonly have a slight fever but the daily rise is usually not over 99 6 or 100 degrees (F) and then it is usually intermittent in type In patients who have a most severe type of pernicious anemia which we observed more frequently before the modern treatment was introduced a high fever was often seen if the red blood cell count was below 1 0 million per cubic millimeter It is advisable however if a patient has only a moderately severe anemia or less to search for some other cause of a febrile reaction which may be present such as a urinary infection if there is a conspicuous elevation

Classification of the Anemias—The classification of the anemias is not entirely satisfactory as is often the case in attempting to systematize our knowledge concerning many disease conditions This is because there are two methods usually employed in formulating a classification one based upon the etiology about which our knowledge is often incomplete and the second the morphological approach which utilizes easily recognizable and definitive information but is necessarily less comprehensive and therefore less useful Nevertheless it is wise to attempt to organize our information concisely as best we can from time to time even if frequent revisions are necessary By so doing our present day knowledge is summarized and made more easily assimilable At least there is one advantage in attempting to classify all allied diseases into one system namely the glaring defects of our knowledge are emphasized and the necessary direction which research work should take becomes more obvious

Morphological Classification of the Anemias —The criteria upon which this classification is based are simple accurate and easily determined They are first the mean corpuscular volume determined by dividing the hematocrit reading by the red blood cell count in millions per cubic millimeter If this is between 86 and 96 cubic microns the anemia is said to be normocytic if it is below 86 cubic microns it is microcytic and if it is above 96 cubic microns it is macrocytic The other determination upon which the classification is based is the mean corpuscular hemoglobin concentration If it is 30 per cent or higher the anemia is regarded as normochromic in nature and if it is below this figure it is considered to be hypochromic

The older determination the color index served a useful purpose and still does if the hematocrit reading is not available It was obtained by dividing the hemoglobin determination in per cent by the per cent reduction in the red blood cells If for example the hemoglobin percentage is 50 per cent and the red blood cell count is 2 5 millions per cubic millimeter (50 per cent of normal) the color index would be Hb/R B C or $50/50 = 1\ 0$ A color index of 1 0 or more indicates a normochromic anemia whereas one below 1 0 is a hypochromic anemia The C I is inferior however to the M C H C both in accuracy of determination and in the information it conveys

It is possible to divide all anemias into three main classes on the basis of the mean corpuscular volume (M C V) and the mean corpuscular hemoglobin concentration (M C H C) These three groups would be 1 the macrocytic anemias of which a classic example would be addisonian pernicious anemia 2 the normocytic anemias such as the anemia of nephritis or chronic infection and 3 the microcytic anemias which are usually due to a deficiency of iron Usually macrocytic anemias are normochromic as are normocytic anemias and almost all of the microcytic anemias are hypochromic *The term hyperchromic anemia is not used* as it is not possible to increase the concentration of hemoglobin in the erythrocyte above normal Red blood cells which are dark staining do not have an increased concentration of hemoglobin but appear so because they are thicker or more spherical in shape These above named groups are the main ones and are therefore of chief importance There are in addition various other combinations For example if a patient with pernicious anemia suffered from bleeding hemorrhoids or some other cause for loss of blood the anemia would be macrocytic and hypochromic

The morphological classification is of importance for two main reasons first by relatively simple and accurate laboratory means it supplies information which is of great assistance from the standpoint of diagnosis For instance a microcytic hypochromic anemia usually means that the patient has an iron deficiency anemia which is almost always due to

chronic hemorrhage either from the gastro intestinal tract or in women from the uterus If the anemia is macrocytic in type it suggests the possibility of pernicious anemia or some allied condition Second by such a classification it is possible to obtain some therapeutic guidance It is known that if the patient has a hypochromia then iron medication is the treatment most likely to produce benefit On the other hand if the anemia is of the macrocytic normochromic type the possibility of treatment with liver extract or vitamin B_{12} should be considered

Additional information concerning the main types of anemia according to a morphological classification is given below

Macrocytic Anemia—Such an anemia is due to a lack of vitamin B_{12} in the diet (nutritional anemia) to a deficiency of the Wills factor which is possibly folic acid to a decrease in the intrinsic factor of Castle (pernicious anemia) to an inefficient absorption of vitamin B_{12} due to gastro intestinal disorders to sprue or to liver disorders with an inability to store vitamin B_{12} It is also the type of anemia seen occasionally in pregnancy which may be on the basis of a folic acid deficiency and in some patients with tape worm (Diphyllobothrium latum) infestation All of the types of anemia mentioned above usually respond either to folic acid or vitamin B_{12} therapy

Normocytic Normochromic Anemia—This variety of anemia is one of the most common types encountered It is usually due to some type of chronic infection or to nephritis with nitrogen retention It is also the variety seen immediately following acute hemorrhage in the hemolytic anemias and myelophthisic anemia in association with leukemia and various forms of cancer with metastatic lesions in the bone marrow The treatment in such patients is to remove the cause and in some instances give blood transfusions In hemolytic anemias certain types of specific therapy are known to be effective in some instances such as splenectomy and treatment with ACTH or cortisone Usually liver extract vitamin B_{12} and iron are ineffective

Microcytic Hypochromic Anemia—This is one of the most common types of anemia encountered It is usually due to chronic hemorrhage either from the gastro intestinal tract or the uterus in women It usually responds dramatically to iron medication In some instances however iron is of no value This is true in the hypochromic anemia of the Mediterranean or Cooley's type the anemia sometimes in Hodgkin's disease and hypochromic anemia of a hereditary nature described by Rundles and Falls (9)

A fourth type of anemia in the morphological classification is included by Wintrobe (2) which he designates as the *simple microcytic type* According to him in such an anemia there are small erythrocytes but little if any decrease in the hemoglobin content per cell He states that this is an ill defined group associated with a great variety of chronic

and non inflammatory diseases as nephritis and infections In the same disorders the anemia may be normocytic which in my experience it has usually been

The classification presented by Ottenberg (*10*) is one based largely on etiology and was made necessary by two important types of investigation The first was under the direction of George H Whipple (*11*) at the University of Rochester and dealt mainly with the response of the anemia of hemorrhage to various diets and other forms of therapy The second dealt with the new information concerning the macrocytic anemias which had as the starting point the studies of Minot and Murphy (*12*) on the treatment of pernicious anemia and of W B Castle (*13*) which were concerned with the etiology of the condition

The following is the original classification as presented by Ottenberg (*10*)

I DEFICIENCIES

A *Iron Deficiency*

1 Blood loss
 (a) Acute
 (b) Chronic
 (c) Hookworm anemia

2 Hypochromic anemia
 (a) Chlorosis
 (b) Simple hypochromic anemia
 (c) Achlorhydric anemia
 (d) Hypochromic anemia of pregnancy

3 Simple nutritional anemia of infants (on exclusive milk diet)
 (a) Anemia of premature infants

B *Deficiency of Antianemic Principle"*

1 Pernicious anemia
2 Sprue
3 Pregnancy pernicious anemia
4 Diphyllobothrium latum (certain cases)

C *Nutritional Deficiencies*

1 Avitaminoses anemia of beriberi pellagra scurvy rickets
2 Loss of bile or of pancreatic secretion
 (a) Bile fistula anemia
 (b) Pancreatic or duodenal fistula
3 Failure of intestinal absorption
 (a) Chronic diarrheas sprue (some cases) celiac disease
 (b) Small intestinal stenosis

4 Nutritional anemia of adults
5 Certain infantile anemias (von Jaksch Cooley)

II INJURY TO THE BLOOD MAKING ORGANS
(Interference with blood regeneration)

A Toxic Destruction of Marrow

1 Aplastic anemia secondary to
(a) X rays radium thorium
(b) *Benzene arsphenamine nitrobenzene trinitro toluene*
(c) Lead, mercury etc
2 Primary aplastic anemia (toxic agent not yet known)

B Mechanical Replacement of Marrow

1 Osteosclerosis
(a) Osteosclerotic anemia
(b) Marble bone disease (Albers Schonberg)
2 Gaucher s and other lipoid deposits in marrow (Niemann Pick Schuller Christian)
3 Leukemia and Hodgkin s disease
4 Metastatic new growths in marrow

C Interference with Blood Regeneration at some Immediate Stage

1 Diseases of the spleen
(a) Banti syndrome (splenic anemia)
2 Diseases of the liver
(a) Cirrhosis
(b) Prolonged obstructive jaundice

III DISINTEGRATION OF BLOOD (*hemolysis*)

A Caused by Hereditary Defects of Red Blood Cells Themselves

1 Hemolytic icterus
2 Sickle cell anemia

B Toxic Destruction of Blood

1 Infections
(a) Bacteria—all varieties especially those invading the blood hemolytic streptococcus Staphylo coccus aureus Streptococcus viridans (bacterial endocarditis)
(b) Protozoa—malaria kala azar syphilis
(c) Acute febrile hemolytic anemia (cause unknown)
2 Intestinal Worms—Diphyllobothrium latum
3 Cancer (including leukemia and allied diseases)
4 Nephritis—azotemia
5 Extensive burns
6 Hemolytic poisons

(a) Serum hemolysins; paroxysmal hemoglobinuria, incompatible transfusion

(b) Chemical: saponin, pyrodine, tolylenediamine, pyrogallol, snake venom, mushroom poison, phenyl hydrazine, potassium chlorate

The following classification is a modification of Ottenberg's which was devised by Dr Frank H Bethell (*14*) and used by him in instructing the undergraduate students at the University of Michigan Medical School

I INCREASED REMOVAL OF CELLS FROM THE CIRCULATION

A *Hemorrhage*

1 Acute hemorrhage

2 Chronic hemorrhage

3 Recurrent hemorrhage

B *Hemolysis*

1 Acute

2 Chronic

(a) Acquired

(b) Congenital

II IMPAIRMENT OF BLOOD FORMATION

A *Deficiencies*

1 Erythrocyte maturing factor (E M F) Pernicious Anemia etc

2 Iron (Copper Manganese)

3 Protein

4 Vitamins (Fractions of B complex)

5 Hormones

B *Destruction of Erythropoietic Cells (Marrow) Aplastic Anemias*

1 Chemicals as arsenic gold benzol and its derivatives

2 Irradiation excessive x ray radium radioactive isotopes

3 Idiopathic

C *Displacement* (crowding out of erythropoietic cells from the marrow)

1 Leukemia (generalized neoplastic disease of the leukopoietic tissue)

2 Primary discrete and disseminated neoplasms of marrow as multiple myeloma chloroma

3 Metastatic neoplasms

(a) Lymphoblastoma

(b) Carcinoma especially of the stomach breast prostate thyroid hypernephroma

(c) Xanthomatosis

(d) Osteosclerosis—marble bone disease

D Depression of Erythropoiesis

1 Infection, chronic

2 Malignancy

3 Nephritis with nitrogen retention

A classification, based in part on one devised for the hemolytic anemias by Estren and Dameshek (*15*) and one concerned with the anemias due to decreased erythrocyte production as formulated by Castle (*16*) is given below

I ANEMIA DUE TO BLOOD LOSS

A Acute Hemorrhage

B Chronic Hemorrhage

II HEMOLYTIC ANEMIAS

A Associated with Intrinsic Abnormalities of Red Blood cells (Hereditary congenital Anemias)

1 With spherocytosis (congenital hemolytic anemias)

2 With target and oval cells (Mediterranean anemia)

3 With target and sickle cells (sickle cell anemia)

4 Others

B Associated with Fundamentally Normal but Damaged Red Blood Cells

1 Injured by extrinsic agents +

(a) Physical (burns roentgen rays)

(b) Bacteria (gas gangrene bartonella)

(c) Parasites (malaria)

(d) Allergens (fava bean)

(e) Chemicals (arsenic sulfonamides)

(f) Immunologic

(i) Anti A anti B

(ii) Anti Rh

(iii) Certain acquired hemolytic anemias

(iv) Certain paroxysmal hemoglobinurias

(v) Others

(g) Siderocytic

(h) Toxic (symptomatic)

2 Destroyed by overactivity of normal hemolytic mechanisms "hypersplenic hemolytic anemia

III ANEMIA DUE CHIEFLY TO DIMINISHED ERYTHROCYTE PRODUCTION

A Nutritional Deficiency

1 Due to decrease in available antipernicious anemia principle (vitamin B_{12})

TABLE II

PER CENT OF PATIENTS WITH MODERATE MODERATELY SEVERE AND SEVERE ANEMIAS IN VARIOUS DEPARTMENTS

(Males Below 78%—12 2 Gm Females Below 70%—10 9 Gm)

		Patients (Per Cent)
1	Urology	12 0
2	Thoracic Surgery	11 7
3	Obstetrics	10 8
4	General Surgery	7 6
5	Gynecology	7 4
6	Oral Surgery	7 1
7	Medicine	6 3
8	Neurosurgery	4 3
9	Otolaryngology	3 7
10	Bone and Joint	2 9
11	Miscellaneous	2 3
12	Ophthalmology	2 1
13	Dermatology	1 9
14	Neurology	1 8
15	Psychotherapy	1 6

TABLE II —The above table shows the incidence of the clinically important anemias in the various departments of the University of Michigan Hospital as determined by an estimation of the hemoglobin in all admissions The most common type of anemia observed was a simple chronic anemia which is usually due to a chronic infection A close second in incidence is iron deficiency anemia which is most frequently due to chronic hemorrhage It is of interest to note that the departments in which anemia is most common are Urology and Thoracic Surgery This is probably related to the high incidence of infections in these departments The relatively few patients with anemia in the department of obstetrics is probably due to the fact that this department is smaller than the one usually associated with a general hospital and the blood examination included here was the one done when the patient was first seen which was usually early in pregnancy It is of interest to note that the incidence of anemia is significant in all departments of the hospital although in many instances blood studies are not usually made For some years a routine estimation of the hemoglobin of all patients coming to the hospital has been done by means of the photoelectric colorimeter It should be kept in mind that this survey included only patients who are 14 years of age or older A separate study is being made of the incidence of anemia in younger patients

(a) From deficient diet (diminished extrinsic factor)
(b) Gastric deficiency of intrinsic factor as in pernicious anemia
(c) Deficiency of intestinal absorption (sprue intestinal stenosis intestinal short circuiting operations)

2 Deficiency of Wills factor (? folic acid)
(a) Defective diet macrocytic anemia of tropics pregnancy ? refractory megaloblastic anemia

3 Iron
(a) Requirements increased by growth
(b) Loss increased by menstruation pregnancy and chronic hemorrhage

(c) Intake decreased by deficient diet achlorhydria diarrhea

B Endocrine Deficiencies

1 Thyroid or pituitary hormones

C Toxic Inhibition

1 External poisons benzol arsenic etc

2 Internal toxins chronic infection renal failure necrotic tumors

D Physical Injury

1 X rays radium radioactive phosphorus

E Mechanical Interference

1 Inadequate marrow capacity anemia of newborn and prematurity

2 Myelophthisis metastatic carcinomatosis primary xanthomatosis leukemia myeloid metaplasia osteosclerosis

F Idiopathic

1 Macrocytic anemia of liver disease (?)

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CHAPTER II

SIMPLE CHRONIC ANEMIA

Introduction —This type of anemia may be defined as a commonly encountered non hemolytic normocytic normochromic anemia due to multiple causes of which the most important is chronic infection It is nearly always mild to moderate in degree and is not characterized by radical variations from the normal blood picture The condition is usually chronic and not ordinarily amenable to any treatment except the removal or control of the underlying cause Such an anemia is found in association with various chronic infections renal insufficiency cancer dysentery certain endocrine disorders as hypothyroidism and Addison s disease and vitamin deficiencies In this section only those types of anemia secondary to chronic infection cancer and renal insufficiency will be considered as they are by far the most important causes to be kept in mind The anemia of hypothyroidism is discussed elsewhere as is that of Addison s disease There is no convincing proof at the present time that a vitamin deficiency per se may be the cause of an anemia Experimental evidence exists however which indicates that vitamin B_6 will cause a hypochromic anemia in animals and possibly further study will demonstrate that other components of the vitamin B complex or other vitamins may be responsible for a diminution in the hemoglobin and red blood cells Although it has been thought by some that a deficiency of vitamin C is of importance in this connection this has not been proven

Incidence of Simple Chronic Anemia —This is one of the most commonly encountered types of anemia throughout the world In a study at the University of Michigan Hospital (*1*) of 11 113 routine admissions to this Institution over a period of about six months it was found that a total of 12 5 per cent had an anemia and of these slightly over one third (39 per cent) were of the simple chronic variety In a great majority of these the anemia was relatively mild as usually the hemoglobin did not fall below 12 3 grams per 100 cc (79 per cent) in males and 11 1 grams per 100 cc (71 per cent) in females Although routine red blood cell counts were not done on all of these patients it is known that as the color index in this variety of anemia is usually about 1 0 the red blood cells would probably vary in numbers between 2 to 4 millions per cubic millimeter

It is known that a very large percentage of patients with such an anemia develop it secondary to chronic infection Malignancy and chronic renal

(c) Intake decreased by deficient diet, achlorhydria, diarrhea

B *Endocrine Deficiencies*

1 Thyroid or pituitary hormones

C *Toxic Inhibition*

1 External poisons benzol arsenic etc

2 Internal toxins chronic infection renal failure, necrotic tumors

D *Physical Injury*

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and streptococcus and staphlococcus hemotoxins produced definite interference with the bone marrow activity in rabbits He suggests that this is an important factor in the production of anemias by bacterial toxins and considers that the mechanism is an inhibition of maturation of the erythrocytes in the bone marrow with a consequent failure of delivery of an adequate number of red blood cells to the peripheral blood

Ample demonstration of the inhibiting effect of infection on the production of red blood cells and hemoglobin is to be found frequently in clinical medicine when patients with pernicious anemia are being treated with antipernicious medication or when iron is given to patients with an iron deficiency anemia In either case an infection of any extent will often lessen markedly the anticipated response to either one of these potent remedies Regardless of the amount of medication which is administered to such patients it is not possible in a great majority of instances to bring the blood to normal until the infection is controlled

The infection most commonly associated with an anemia of this type is a mild chronic variety which continues over a long period of time Among the more common forms are those involving the urinary tract and the pelvis rheumatoid arthritis and chronic pulmonary infections such as bronchiectasis or lung abscess A very mild anemia is commonly observed in long continued pulmonary tuberculosis but this is often so slight in extent as to be disregarded Severe anemias are not common in this disease in my experience unless there have been repeated and extensive hemoptyses In about three fourths of the patients with subacute bacterial endocarditis due to a streptococcus viridans infection there has been a moderate anemia of this type and in the remainder it has been more severe In chronic brucellosis such an anemia is commonly encountered (5) Many other types of chronic infection may be responsible for an anemia of this nature but in my experience focal infection has not been of great importance Occasionally in a growing child a chronic infection of the sinuses may be of significance but inactive foci about the teeth apparently do not play an important role

In a long series of animal experiments and clinical observations Wintrobe Cartwright and their co workers have studied the mechanism responsible for the anemia of infection (6) They conclude that in such cases there is a striking reduction in the blood plasma iron the serum copper is elevated the erythrocyte protoporphyrin is increased from two to 14 times normal and the coproporthyrin excretion is increased Furthermore it was discovered that the level of the plasma iron could not be raised by the oral administration of iron or by giving iron binding protein The low plasma iron however was observed to return to a normal level after the control of the infection and disappearance of the anemia They also reported that a low plasma iron developed in dogs following the injection of staphlococci or turpentine intramuscularly

insufficiency also play a significant but less important role in the etiology of the above group The other causes of simple chronic anemia, previously mentioned only occasionally account for the condition It should be re emphasized therefore that the most frequent cause of one of the most common varieties of anemia is chronic infection

ANEMIA ASSOCIATED WITH INFECTION

The Cause of Anemia in Infection —Infection may cause anemia by two different mechanisms, one an increased destruction of blood as seen occasionally in the septicemias and the other, which is far more common is associated with a depression of the bone marrow The latter type is probably the most frequent form of anemia encountered in clinical medicine although it is often mild in degree

There is abundant evidence that such a non hemolytic anemia of infection is due to diminished blood formation In the standard anemic dog Robscheit Robbins and Whipple (2) found that an endometritis lasting over weeks due to the colon bacillus, profoundly reduced the hemoglobin production Likewise they observed that a sterile abscess decreased its production in an anemic dog when liver was being fed During a fasting period the infection reduced the hemoglobin formation to zero They concluded from their studies that the diminished formation of hemoglobin in animals with infection or in whom a sterile abscess has been produced is due to a disturbance in the internal metabolism relating to hemoglobin formation The belief was expressed that this same mechanism is of importance in humans No indication of significant red blood cell destruction or impaired absorption of food was observed in their experimental animals

Vaughan and Saifi (3) found no evidence that the bone marrow in patients with an anemia dying of a long continued infection is hypoplastic On the contrary their studies indicate that it is hyperplastic in nature Hence in their opinion the anemia is not due to aplasia of the bone marrow Furthermore in these cases there is no increased excretion of urobilinogen and therefore no evidence that the red cells are destroyed in greater numbers than normal In considering faulty red blood cell formation as a possible explanation of this variety of infection they emphasize that neither marrow aplasia nor excessive hemolysis can be demonstrated In support of their explanation they report their studies on the porphyrin excretion which shows an increased production of coporphyrin I and II This they interpret as indicative of some abnormality of hemoglobin synthesis dependent upon the presence of infection

Further support of the view that diminished blood formation is probably the cause of the anemia associated with infection is to be found in the work of Willison (4) who reports that tetanus and diptheria toxins

and streptococcus and staphlococcus hemotoxins produced definite interference with the bone marrow activity in rabbits. He suggests that this is an important factor in the production of anemias by bacterial toxins and considers that the mechanism is an inhibition of maturation of the erythrocytes in the bone marrow with a consequent failure of delivery of an adequate number of red blood cells to the peripheral blood

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It is established beyond the slightest question of a doubt, therefore that in an infection there is a definite disturbance in iron metabolism as indicated by the above studies They concluded also that the low plasma iron was due mainly to a rapid removal of iron from the blood stream rather than to poor absorption although some decrease in this latter process occurs when iron is given orally

It has been shown that the injection of large amounts of iron given intravenously to patients with an anemia of infection does not benefit the anemia or raise the plasma iron content (7) The cause of the lowered plasma iron is not because the inflammatory tissue which is known to have an affinity for iron, removes it from the blood stream rapidly as it has been shown that when radioactive iron is injected into animals in which inflammation has been produced the greatest proportion of iron is diverted to the liver and spleen rather than the inflamed areas (8)

It must be concluded for the present, therefore that the cause of anemia of infection is not entirely known Certainly there is a disturbance of metabolism of which the demonstrated changes in the iron metabolism play an important role as indicated by the low plasma iron

It is suggested by Vaughan (9) that the anemia of infection may be dependent on a disturbance of hemoglobin synthesis affecting chiefly the globulin element The deficiency of globulin may be part of a wide disturbance of protein metabolism dependent upon the action of break down products liberated from injured tissues or by the need of such tissues for certain amino acids Preliminary studies suggest that cobalt may be concerned at some point in this chain of events but caution should be used in accepting this inference until more human cases have been studied

Symptoms and Physical Signs —The symptoms and signs associated with such an anemia are slight if any The degree of anemia is often so mild that the clinician sometimes attributes the slightly reduced red blood cell count and hemoglobin percentage to a technical error and disregards it as unimportant Rarely is the anemia so severe as to cause pronounced dyspnea palpitation or pallor In my opinion however it very definitely in combination with other factors such as toxemia contributes materially to fatigue and an impaired sense of well being in many patients Furthermore it undoubtedly prolongs the period of convalescence

Changes in the Blood —An anemia of this variety is usually very mild the red blood cell count most commonly being between 3 5 and 4 0 millions and the hemoglobin between 10 and 11 grams per 100 cc although in some cases it may be as low as 7 0 to 8 0 grams It is usually of the normochromic and normocytic type with a high color index The mean corpuscular hemoglobin concentration is 30 per cent or more and the saturation index 0 91 or higher Observation of a stained blood film rarely

shows changes of importance in the erythrocytes although when the anemia is severe there may be slight anisocytosis but rarely is poikilocytosis noticeable. The reticulocytes are usually below 1.0 per cent but occasionally they may be slightly higher. An increase in the total white blood cell count is infrequently observed and when present is usually associated with an acute exacerbation of the chronic infection. There are no important changes in the number of the blood platelets.

In some patients especially those with subacute bacterial endocarditis and acute rheumatic fever I have seen severe anemia develop. In the former disease the red blood cell count may fall below 2.0 millions per cubic millimeter with a proportionate drop in the hemoglobin percentage. A more detailed account of the changes in the blood in these conditions is given under the appropriate sections which follow.

Hemolytic Anemias Due to Infection.—The importance of the role of infections which cause anemia by increasing the hemolysis of blood has undoubtedly been over emphasized in the past. The undeniable knowledge that powerful toxins can destroy red blood cells in the circulating blood and hence cause an anemia has served too often as the basis for speculation which has been the erroneous explanation of various types of hemolytic anemias. William Hunter in 1888 emphasized the hemolytic nature of pernicious anemia and suggested that it was due to a mixed infection with bacteria including the streptococcus which were found in chronic infective lesions of the mouth, stomach and intestines. This theory, long ago discredited, along with the knowledge that powerful hemolysins can be elaborated by other bacteria, as Witts says (*10*) "has prejudiced the approach to the problem and prevented the orderly accumulation of facts."

It is known that a hemolytic anemia may be the result of a variety of bacterial infections although as previously stated they are not a common cause as has been assumed in former years. It is exceedingly rare for ordinary streptococci to cause an anemia of this type but anaerobic streptococci may be the etiological agent in association with such conditions as puerperal fever. Undoubtedly the organism which is of the greatest recognized importance in the causation of a hemolytic anemia is Clostridium welchii. It has been shown to cause an anemia in rabbits which Cornell (*11*) attributed to a direct action of the exotoxin produced by this organism on the erythrocytes. This reaction is said by this investigator to occur in vitro with washed red blood cells. An infectious anemia has been produced experimentally by Clostridium welchii in rabbits by Reed, Orr and Burleigh (*12*) and in monkeys by Kahn and Torrey (*13*).

When these observations were considered with the fact that Clostridium welchii is found in significantly increased numbers in the stool of patients with pernicious anemia it was assumed by some that the anemia

of this condition might be attributed to the action of the toxin of an organism which was known to cause an increased destruction of erythrocytes (*14*) The generally accepted present day view that pernicious anemia is not due primarily to increased hemolysis of blood, and the observation by Nye (*15*) that an equal or even greater increase of Clostridium welchii could be demonstrated in the stools of persons with uncomplicated achlorhydria and a normal blood has relegated this theory to the background Recent observations on the growth of bacteria in the upper gastrointestinal tract in patients with pernicious anemia and a reticulocyte rise following the administration of aureomycin create a new interest in this relationship (see section on Etiology of Pernicious Anemia) *It has been shown however that Clostridium welchii could be responsible for an anemia of the hemolytic type In gas gangrene due to this organism a striking anemia may develop within a few days Along with* this there is a frank jaundice a reticulocytosis the appearance of nucleated red blood cells in the circulating blood a striking leukocytosis with an increased percentage of neutrophils and a few myelocytes In extreme cases the blood may be destroyed with such rapidity that a hemaglobinuria develops With the control of the infection there is a rapid recovery from the anemia

Although it is recognized that a hemolytic anemia may be due to a variety of organisms (*16*) care should be used in accepting a positive blood culture as a cause of an anemia in any given patient It should be kept in mind that patients with anemia often have a low resistance and hence are susceptible to infections of various types The presence of organisms in the blood stream of any given patient may be the result rather than the cause of an associated anemia For example hemolytic anemia has been attributed to typhoid fever but as Witts (*10*) points out it is *possible in some of the reported cases that the anemia was an Addisonian type rather than due to a hemolysin*

In 1925 Lederer (*17*) described a group of cases of *acute hemolytic* anemia which he thought were *possibly due to an infection* It has not been demonstrated however that the *hemolysis responsible for the* anemia is due to a micro organism In the *opinion of Dameshek and* Schwartz which is now generally accepted infection plays *no role in the* production of an anemia of this type Other observers as *Parsons and* Hawksley (*18*) state that there is no certain knowledge of *the etiology* of this type of anemia as the infecting agent has not *been discovered* A full discussion of Lederer's acute hemolytic anemia is *given in the sec*tion on Hemolytic Anemias (p 169)

There can be no question but what an acute hemolytic anemia may develop during the course of an infection due to the *streptococcus* It should be kept in mind however that some *unknown conditioning fac*tor may be present before an anemia will develop *A typical example of*

a hemolytic anemia due to a streptococcus septicemia is reported by Greenthal (*19*) as follows the patient a male of 23 months when first observed had an acute inflammation of the tonsils pillars and fauces with peritonsillar swelling and an acute cervical adenitis A throat culture showed a mixed infection with streptococci present The red blood cell count was 2 0 millions per cubic millimeter and the hemoglobin 5 5 grams with a color index of 1 1 There was marked anisocytosis and poikilocytosis The leukocyte count was 34 700 per cubic millimeter with 78 per cent neutrophils The icterus index was 30 A few days later the reticulocytes were 7 8 per cent A positive blood culture for hemolytic streptococci was obtained Recovery followed the use of sulfanilimide and five blood transfusions

From my own personal experience and from a review of the literature *I must conclude that hemolytic anemias due to infection are not commonly encountered in clinical medicine and their importance has been overestimated* On the other hand it must be acknowledged that streptococci may occasionally be responsible for such an anemia and Clostridium welchii commonly produces it Undoubtedly it may be due occasionally *to other organisms It should be kept in mind however that a positive* blood culture does not always account for the cause of the anemia which may be present My opinion concerning the importance of infection as a cause of hemolytic anemia is ably expressed by the statement of O H Perry Pepper (*20*) who says Bacterial toxins such as that of the gas *bacillus of Welch undoubtedly cause hemolytic anemia in some infec*tions but there is much doubt and speculation as to how active in this respect other less virulent bacteria are It is tempting but unjustified to attribute the anemia of many infections to a hypothetical hemolytic toxin"

Changes in the Blood in Rheumatoid Arthritis and Allied Conditions — In a great many patients in whom this condition has been established for some time there is a mild anemia which is most commonly normocytic and normochromic in type In some instances however it may be microcytic and hypochromic in nature The reticulocytes the icterus index *and blood bilirubin and the urinary excretion of urobilinogen* are normal or they may be actually decreased The bone marrow shows an increased number of normoblasts and pronormoblasts Anemia when present is usually in those patients in whom the sedimentation rate and body temperature has been elevated for a considerable period of time Hence *it is generally agreed that the reduction* in red blood cells and hemoglobin is the result of inhibition of erythropoiesis and impaired synthesis of hemoglobin as a result of infection It has been suggested (*20*) that it may also be associated with a dietary deficiency and interference with absorption from the intestines in some cases but it is not known how im*portant a role these factors* play

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Changes in the Blood in Rheumatoid Arthritis and Allied Conditions — In a great many patients in whom this condition has been established for some time there is a mild anemia which is most commonly normocytic and normochromic in type In some instances however it may be microcytic and hypochromic in nature The reticulocytes the icterus index and blood bilirubin and the urinary excretion of urobilinogen are normal or they may be actually decreased The bone marrow shows an increased number of normoblasts and pronormoblasts Anemia when present is usually in those patients in whom the sedimentation rate and body temperature has been elevated for a considerable period of time Hence it is generally agreed that the reduction in red blood cells and hemoglobin is the result of inhibition of erythropoiesis and impaired synthesis of hemoglobin as a result of infection It has been suggested (20) that it may also be associated with a dietary deficiency and interference with absorption from the intestines in some cases but it is not known how important a role these factors play

The white blood cell count is usually normal in the chronic cases but in those patients with an acute febrile onset, a leukocytosis varying from *12 000 to 20,000 per cubic millimeter is common With the leukocytosis* there is also an increase in the number of polymorphonuclear neutrophils to 75 or more per cent The Schilling hemogram in these cases shows a shift to the left indicating that an increased number of young neutrophils are present which is suggestive evidence that an effort is being made on the part of the bone marrow to overcome an infection Even in the chronic cases with only a slight rise in body temperature above normal there is almost always an increase in the young neutrophils over the normal number as indicated by an abnormal filament nonfilament ratio Normally the number of nonfilamented neutrophils is regarded as varying from 6 to 16 per cent of all the neutrophils in the circulating blood It is stated by Farrar and Rayburn *(21)* that a normal nonfilament count usually excludes rheumatoid arthritis While this statement is extreme, judging from my own experience nevertheless it is *unusual* to observe a normal nonfilament count of the neutrophils in patients with this condition *when the disease is active*

The authors just cited state that in patients with slight fever, the white blood cell count is usually between 4000 and 11,000 per cubic millimeter Even when the differential count is normal the nonfilamented neutrophils are usually increased when activity of the disease is present Among the 234 cases of rheumatoid arthritis which they collected from the literature 147 showed a nonfilamented count of more than 16 per cent and of 392 cases the count was greater than 8 per cent in 346 cases In their opinion, in a patient with chronic rheumatism an increased nonfilamented count usually suggests the possibility of rheumatoid arthritis a mixed form of arthritis with rheumatoid features an osteoarthritis with a superimposed active infection or a suppurative arthritis

Detailed hematologic observations by Finch and his co workers (*22*) were made on a group of patients with rheumatoid arthritis and allied disorders (a few cases of periarteritis nodosa and scleroderma) who received either ACTH or cortisone They report the following results a significant reticulocytosis occurred with an increase in the hematocrit reading and the total red blood cell mass in all patients who responded clinically to ACTH or cortisone There was a moderate depression of the erythroid series in the bone marrow before treatment but a return to normal at the end of therapy There was a significant polymorphonuclear leukocytosis a less well sustained lymphopenia and a depression of the circulating eosinophils during treatment Before treatment there was a normal or increased number of eosinophils in the bone marrow During therapy there was no change in their numbers in the bone marrow despite a profound peripheral eosinopenia They conclude that in an anemia associated with an inflammatory disease a favorable response

from ACTH or cortisone is probably due to a control of the underlying cause rather than to a primary "stimulation" of the bone marrow

Changes in the Blood in other Forms of Arthritis—Anemia is uncommon in osteoarthritis (hypertrophic) When present it usually indicates some complication in which the association may be fortuitous Likewise the total and differential white blood cell counts are normal unless some complicating infection is present It has been reported by Hartung and his associates (*23*) that the nonfilamented count may be elevated in some cases of osteoarthritis the average being 21 6 per cent which indicated a very slight rise The average count in six cases of rheumatoid arthritis was definitely greater as it was 29 6 per cent

The increased nonfilament count has been attributed by Collins (*24*) to the presence of large cystic areas in the region of the femur or in the acetabulum in cases of malum coxae senilis It is suggested that aseptic necrosis in these cytic areas might account for this change in the neutrophils but Farrar and Rayburn (*21*) comment that if this is the explanation it is unusual that the sedimentation rates should be normal

Blood Changes in Fibrositis—It is reported by Slocumb (*25*) that there are characteristically no important changes in the blood in patients with fibrositis According to this author there is no anemia no leukocytosis no increase in nonfilamented neutrophils or in the sedimentation rate Farrar and Rayburn (*21*) report that in 112 cases of the 149 collected from the literature the sedimentation rate was normal In the remaining 37 cases there was only slight and sometimes questionable increases in the rate The Arneth count was reported as normal in 104 cases of the disease (*24*)

Morphological Changes in the Blood in Gout—Anemia does not develop in gout unless some associated disease is present which might account for it (*26*) It is usual however to find that the total white blood cell count is increased in an acute attack of gout and the differential count regularly shows a greater number of neutrophils than normal It has been found by Gibson and Kersley (*27*) that the nonfilamented forms of the neutrophils are as much increased in gout as in cases of rheumatoid arthritis

Suppurative Arthritis—In this condition there is a neutrophilic leukocytosis with a greater number of filamented forms than normal and a striking increase in the sedimentation rate An anemia may appear as the result of the infection if the process persists for some time

Gonorrheal Arthritis—During the acute attack there is frequently a leukocytosis reaching as high as 20 000 or more per cubic millimeter With this there is also an increase in the neutrophils to 70 or 80 per cent or more Ordinarily an anemia is not present If observed in any given patient it is usually due to some complication which is not related to the joint infection

Neutropenia in Patients with Chronic Arthritis—It is emphasized by Farrar and Rayburn (*21*) that a decrease in the total white blood cell count with a diminution in the per cent of neutrophils is not rare in patients with chronic rheumatoid arthritis although the cause of this is obscure. Perhaps the most striking examples of neutropenia are seen in patients who present the syndrome of arthritis anemia and an enlarged spleen (Felty s syndrome) In some instances patients with rheumatoid arthritis in whom emaciation is a feature have a normal white blood cell count but a decrease in the percentage of neutrophils and of nonfilamented forms Other possible causes of neutropenia in rheumatoid arthritis as mentioned by Farrar and Rayburn are malnutrition allergy endocrine dysfunction and drug idiosyncrasy They claim that leukopenia is frequently observed in simple malnutrition and that both an inadequate dietary intake and impaired absorption exist in patients with rheumatoid arthritis It is mentioned by these observers that neutropenia may be present in adrenal and ovarian insufficiency. Even though the cause of the neutropenia cannot be determined they state that massive liver therapy both orally and parenterally is often effective

Treatment of the Anemia of Arthritis—In rheumatoid arthritis there is usually no effective treatment of the anemia except those measures directed toward the removal of the underlying cause of the arthritis Unfortunately we do not possess any specific form of therapy for this malady but in my experience the injection of gold salts has often resulted in striking improvement in these patients Not only are the symptoms referable to the joints less prominent but with this there is usually an improvement in the anemia Liver and iron have not been helpful in these cases with rare exceptions If a hypochromic anemia is present a full course of iron in the form of ferrous sulphate 0 3 to 0 6 gram three times daily after meals is indicated According to Farrar and Rayburn (*21*) blood transfusions may exert a dramatic effect They quote Thompson Wyatt and Hicks (*28*) as claiming that clinical improvement was progressive in two thirds of the cases which received blood transfusions Pemberton and Bach (*29*) state that the course of the disease is shortened by the transfusion of 250 to 500 cc of blood weekly for two to six weeks

In the treatment of anemia it is wise to adjust the patient s diet in order to insure a minimum protein intake of approximately 1 to 1 5 grams per kilo of the patient s ideal body weight daily This should include eggs lean meat and milk daily Also attention should be given to the patient s vitamin intake

As mentioned elsewhere (see p 22) ACTH and cortisone exert a temporary beneficial effect on the anemia

Anemia in Rheumatic Fever—In this condition often a moderate to severe anemia develops during the active phase of the disease As the infection subsides the red blood cell and hemoglobin levels usually return

to normal gradually Careful studies have shown that the presence of an anemia is a valuable indication of continued rheumatic activity (28)

There is every reason to believe that the main factor in the development of the anemia is diminished blood formation (30) based on the observation that the icterus index and reticulocyte levels are usually normal. It has been observed by Hubbard and McKee (30) however that frequently in the recrudescences of the disease there is a slight but significant increase in the reticulocytes of the circulating blood usually varying from 4 to 6 per cent Such a rise is likely to occur shortly after the period of greatest activity of the disease It has been noted also during the gradual subsidence of the recrudescence but at a time when the low grade fever and the increased sedimentation rate continued or when the disease process appeared quiescent In their opinion this seemed to indicate that there is a suppression of erythropoiesis during the height of disease activity and that when this subsides there follows an augmented red blood cell formation as shown by the increase in the circulating reticulocytes

Whether or not depression of erythropoiesis is the sole factor in the causation of the anemia remains an open question as the rapidity with which it develops suggests that there may also be increased blood destruction This view finds some support in the work of Kapp and Coburn (31) and also in the observations of Hubbard and McKee (30) The latter observers found that a considerable number of their patients during recrudescences showed minor increases in the blood bilirubin and icterus index As there was no consistent apparent correlation between the degree of activity of the disease and the amount of serum bilirubin and as there were no constant variations in the consecutive readings during the course of an exacerbation one cannot be certain that such changes are indications of increased blood destruction The same may be said of the increased urobilinogen excretion in the urine which is generally observed during the periods of activity of the disease as this might be due to the often associated congestive heart failure with passive congestion of the liver In general it is safe to state that during exacerbations of rheumatic fever there is often a rapidly developing anemia of moderate degree and hence its presence may often be an indication of disease activity which should be added to other such criteria as fever increased sedimentation rate and leukocytosis

The principal cause of this anemia appears to be a suppression of the normal rate of red blood cell formation but the possibility cannot be excluded that increased red blood cell destruction may also play a significant role in its production The typical blood changes may be described as follows the red blood cell count often falls from a normal level to the vicinity of 3 0 to 3.5 millions per cubic millimeter and there may be a drop in the hemoglobin reading from 85 to 60 or 70 per cent Often the

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Almost always the anemia is of the hypochromic type with a color index which is usually in the vicinity of 0 70 and a mean corpuscular hemoglobin concentration between 28 and 30 per cent The red blood cell size as indicated by the mean corpuscular volume is usually at the lower limits of normal or slightly below normal In most of the cases I have seen it has been between 82 and 96 cubic microns although occasionally it has been below 80 cubic microns

The white blood cell count in this condition is variable but it is now generally agreed that when a leukocytosis is present it is strongly suggestive evidence that some complication is present Such complications leading to a leukocytosis are listed in order of frequency by Pepper (33) as follows 1 gross infarction 2 post transfusion reaction 3 phlebitis 4 severe cardiac failure 5 serum reaction 6 pneumonia and 7 unexplained This author concludes that apparently a leukocytosis in these patients seldom if ever occurs in subacute streptococcus viridans endocarditis except following infarction embolism or other complications This has been in accord with my own experience for most of the white blood cell counts in these patients have been 6000 to 10 000 per cubic millimeter unless some complication is present and this is usually embolic in nature When this has occurred the white blood cell count has usually risen to between 12 000 and 22 000 per cubic millimeter At these times there has also been an increase in the neutrophils to the neighborhood of about 80 per cent or more A study of the basophilic granulation in the neutrophils shows that this change is not pronounced in most instances the usual observation being that it is slight or moderate

In occasional instances there may be a leukopenia with a white blood cell count below 4000 per cubic millimeter or less In one of my patients it fell to 1600 per cubic millimeter with a neutrophil percentage of 9 but this was accounted for on the basis of a true attack of agranulocytosis which was attributed to sulfapyridine therapy Occasionally a leukopenia may occur in these patients with no other explanation than the possibility that there is an overwhelming infection and the granulopoietic elements of the bone marrow are unable to respond adequately

It has been reported by various observers (33) that there is sometimes a great increase in monocytes of the circulating blood and macrophages may be observed in some instances It is not rare in my experience to observe a monocytosis in which these cells reach 20 to 25 per cent although their presence or absence is not constant enough for such a change to be of diagnostic significance Since the report of Sampson Kerr and Simpson (34) in 1923 I have made a great effort in each case observed to identify the monocytic cells which they termed macrophages in the circulating blood They describe these cells as varying in size from 10 to 18 microns and fluctuating in number in the peripheral blood from 0 to 48 per cent The nucleus is round oval indented or multiple These

color index is below normal, indicating a hypochromia. There are no striking changes in the cell size or the mean corpuscular hemoglobin concentration but in general they may be said to vary from normal to low values. Hence the anemia may be considered to be of a normochromic or hypochromic and normocytic or microcytic type.

The changes in the white blood cells have long been recognized as a valuable index of the progress of the infection. During the active phases of the disease the white blood cell count is usually between 15,000 and 20,000 per cubic millimeter and occasionally it may reach even higher levels. In the polycyclic and continuous forms of the disease there is often a persistent but slight leukocytosis, usually varying from 12 000 to 14 000 per cubic millimeter, which is an indication of the continuation of the disease process. It is claimed that a leukocytosis may be suppressed by antipyretic therapy (32).

Treatment of the Anemia of Rheumatic Fever.—There is no effective treatment for this type of anemia except that directed toward the underlying cause of the disease. Although it is not often that the anemia reaches a severe grade it should be emphasized that it does constitute a further source of cardiac embarrassment to a heart which is frequently already damaged. Rarely, however, is the anemia so severe as to indicate the advisability of blood transfusions and unless there is some complication such as bleeding iron is not of value nor is liver extract or folic acid. There is usually a fairly prompt disappearance of the anemia when the infection subsides and its persistence, therefore, is often an indication of continued activity of the rheumatic infection.

Changes in the Blood in Patients with Subacute Streptococcus Viridans Endocarditis.—It is generally accepted that an anemia develops eventually in almost all patients with this disease and there may or may not be a leukocytosis and a monocytosis. There has not been reported in the literature however to my knowledge a large series of carefully studied cases in which the infecting organism has been identified and careful blood studies have been made giving among other observations the hematocrit reading upon which to calculate the mean corpuscular volume and the mean corpuscular hemoglobin concentration.

A series of 20 cases due to an identified nonhemolytic streptococci has been reported by Pepper (33) but hematocrit readings are not recorded. He concludes that an anemia with a color index below one is the rule in the condition the anemia tends to increase as the disease progresses and it may become very severe. In my own experience the red blood cell count is usually in the vicinity of 3 5 millions per cubic millimeter and the hemoglobin about 50 per cent (7 8 grams). In some instances however the red blood cell count may be normal and in others it may be as low as 2 0 millions per cubic millimeter or less. In general I agree with Pepper (33) that the anemia tends to advance as the disease progresses.

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stenosis which may have a more specific effect on the peripheral blood and (4) the coincidental occurrence of anemia due to unrelated causes such as that due to menorrhagia or metrorrhagia In this connection it is of interest to note that pulmonary tuberculosis is rarely associated with pernicious anemia although the two diseases occasionally do exist coincidentally Barron (35) has emphasized the fact that there may be an antagonism between the two conditions

Braverman (36) has made an extensive study of 509 patients with pulmonary tuberculosis in which 9 6 per cent were classified as minimal 15 5 per cent as moderately advanced and 74 8 per cent as far advanced It was found that 30 2 per cent of the entire group had an anemia This statement was based on the acceptance of the lowest standards of normal for men of the red blood cell count as 4 6 millions per cubic millimeter and the hemoglobin 14 62 grams per 100 cc of blood and for females the same standards were employed for hemoglobin but the lowest normal red blood cell count was regarded as 4 2 millions per cubic millimeter

In this group it was determined that 10 3 per cent had a normocytic hypochromic anemia 15 0 per cent had a microcytic hypochromic anemia and 4 9 per cent had a microcytic normochromic anemia The author concludes that a microcytic hypochromic and normocytic hypochromic anemia occur most often During the early stages of the tuberculosis lesion the first indication of an anemia may be only an achromia of the erythrocytes but sooner or later microcytosis appears Often the two are noted together if the infection is severe Both the size and hemoglobin content of the red blood cells decrease as the severity and activity *of the tuberculosis increase*

It is pointed out by Braverman (36) that as pulmonary tuberculosis is characterized by periods of stability retrogression or progression the frequency of anemia and its character therefore vary with the changing lesion Furthermore complications have a varied effect on the blood picture for in terminal states there may be either a hypochromic anemia or a normal red blood cell picture which has been known to have been present throughout the illness The anemia often becomes severe however in the presence of intestinal tuberculosis and diarrhea It is concluded by Braverman (36) in summary that the anemia in the presence of the complications of pulmonary tuberculosis is most often hypochromic and microcytic and differs chiefly in degree If the acute pulmonary lesion is accompanied by sepsis the severity of the anemia increases rapidly This is often less marked in the case of amyloid disease The importance of complicating disease to the anemia in pulmonary tuberculosis is emphasized in the statement made by this author to the effect that it often reduces the blood from the lower limits of normal to that of a definite anemia and that in the group which he studied over 50 per cent of patients with a significant complication had an anemia

cells show a striking tendency to phagocytosis and they are often observed with vacuoles containing engulfed red and white blood cells possibly bacteria and unidentified material in all stages of disintegration With Giemsa s stain prominent fine azurophilic granulation of the cytoplasm may be demonstrated All types of intermediate forms varying from the cells just described to the typical normal monocyte of the circulating blood are observed I have usually found these cells to be present at least in small numbers in almost all patients during the active stages of the disease They cannot always be demonstrated in all such cases however unless a prolonged search is made by an experienced observer Their presence is strongly suggestive of the diagnosis of subacute streptococcus viridans endocarditis but it should be kept in mind that they may occur in other conditions such as typhoid fever malaria and various bacteremias (33) Furthermore their absence from the blood stream cannot be considered important evidence against the diagnosis of this malady

In my experience there does not appear to be any important or constant changes in the number of the platelets of the circulating blood in this condition In most instances they are recorded as being present in normal or adequate amounts but occasionally they have been reported as being slightly increased in numbers

In summary then it may be said that there is often a hypochromic and usually a normocytic or slightly microcytic anemia present in subacute streptococcus viridans endocarditis which tends to become more severe as the disease progresses Leukocytosis generally with an increase in neutrophils is variable and when present it should be interpreted as probable evidence of embolic phenomena Macrophages are observed in the circulating blood in most instances during the active phases of the disease and they may be found provided a thorough search is made for them by an experienced observer The monocytes of the blood may be increased but this is not a constant feature of the condition There is no important change in the blood platelets Basophilic stippling of the neutrophils is slight which would indicate that the virulence of the organism is not great

Anemia in Pulmonary Tuberculosis—Ordinarily anemia is not an outstanding feature in the clinical picture of pulmonary tuberculosis although it may be present in some patients It is usually of a mild degree but occasionally severe forms may develop

In considering the anemia of this disease there are several factors which must be taken into consideration namely (1) the effect of the prolonged chronic febrile infection with exacerbations and remissions (2) the influence of certain complications such as tuberculous enteritis empyema amyloid disease Addison s disease and others (3) the changes produced by various complications as repeated hemoptyses or intestinal

anemia Intestinal hemorrhage is present to some extent in every case of chronic ulcerative colitis during a greater portion of the active stage of a patient s illness In some instances the bleeding may be so severe that the stools appear in the gross to be made up largely of blood When such bowel movements amount to 10 or 15 daily or more it is to be expected that such an extensive loss of blood will result in an anemia In a majority of cases however there is usually a small or moderate amount of blood loss which may be observed by inspection of the stools in the gross When the stools appear normal there is frequently a positive test for occult blood which may be present daily for long periods of time dur ing the active phases of the disease or even when the patient may be showing signs of improvement The continuous loss of occult blood alone over long intervals even in the absence of gross hemorrhage may result in a microcytic hypochromic anemia of considerable extent

Other Etiologic Factors—Another factor of considerable importance in the causation of the anemia is the impaired absorption from the gastro intestinal tract This may be associated with various abnormalities such as the presence of a hypoacidity or anacidity which interferes with the normal absorption of iron Another factor may be the rapid passage of the intestinal content through the gastro intestinal tract which results in the inefficient absorption of iron and perhaps vitamin B_1 and folic acid In the case of lessened absorption of iron a hypochromic anemia would result and when there is a deficiency in the amount of erythrocyte matur ing factor a macrocytic anemia may develop

The frequency of hypochlorhydria or anacidity in patients with chronic ulcerative colitis following injection of histamine is said by Mackie (37) to be about 40 per cent of all cases It appears logical to assume that there may be hypermotility which may account for the impaired absorp tion and presence of an anemia One patient whom I observed a boy of 16 passed carmine through his bowel in an average time of 30 minutes According to Mackie (37) identical changes are present in chronic ul cerative colitis as those observed in sprue and these may be demonstrated by means of x ray It is known that in the latter disease there is defi cient absorption from the intestinal tract

Of considerable importance from the standpoint of the cause of the anemia in this condition is the deficient food intake which is so com monly present in patients with this condition This arises from two reasons one it is difficult to obtain a satisfactory iron intake on a low residue diet which is frequently prescribed in this condition Second patients with this disease often have an impaired appetite hence the ingestion of an improper diet is likely over a long period of time From the standpoint of the anemia the diet is important for the lack of proper iron and probably also a diminished protein intake especially milk eggs and meat The former undoubtedly in some cases contributes to the

In consideration of the figures presented by Braverman, it is possible to arrange them in the following manner

Accepting the hemoglobin standards which we employ at the Simpson Memorial Institute as normal (12 0 grams or 78 per cent for women and 13 0 grams or 82 per cent for men as the lowest limits of normal) the following statement can be made in males with minimal tuberculosis, there were no cases with anemia, in those with moderately advanced lesion 10 5 per cent had an anemia, in those with far advanced lesions 19 per cent had an anemia In females the incidence of anemia in the three groups was 11 per cent 23 per cent and 19 7 per cent in the order of severity as stated above

Treatment of the Anemia Associated with Pulmonary Tuberculosis — It is emphasized (36) that multiple factors must be dealt with in the management of this condition They are (1) adequate control of the disease itself (2) an ample diet with special attention to vitamins and proteins especially fresh meats and (3) the administration of iron It is stated by Braverman (36) that if the course of the tuberculosis is favorable and uncomplicated the anemia will usually disappear in about three to six months If the therapeutic response to iron is absent or suboptimal then one should suspect intestinal tuberculosis a continued activity of the pulmonary lesion the presence of any one of the complications such as pleurisy anorexia unreported hemoptyses the loss of blood from some source as hemorrhoids or that iron is not being taken in adequate doses

The Blood in Non specific Chronic Ulcerative Colitis —The usual findings in the blood of patients who have this condition is a moderate anemia with an erythrocyte count in the vicinity of 3 0 to 3 5 millions per cubic millimeter and a hemoglobin of 6 2 to 7 8 grams a normal leukocyte count in the absence of complications and the changes in the white blood cells where are commonly associated with severe infections The latter are an increase in the nonfilamented count above 16 per cent the presence of toxic granulations in the neutrophils an increase in the percentage of the latter cells over normal and a shift to the left in these cells

An anemia is to be anticipated in these patients but it is somewhat surprising that it is not always present in some in whom the disease may be fairly well advanced Anemia is to be expected because there are so many factors associated with the condition which are commonly accepted causative factors namely 1 chronic hemorrhage 2 a deficiency in diet 3 impaired absorption either as the result of a hypoacidity or an achlorhydria or increased motility of the bowel and 4 the inhibiting effect of infection on the synthesis of hemoglobin and the formation of the red blood cells

The Role of Chronic Hemorrhage —Undoubtedly the loss of blood from the bowel plays the most important role in the causation of the

relatively large amount of blood and because the greatest diminutions of erythrocytes and hemoglobin are often associated with the more severe infection and the most inadequate food intake

Treatment of the Anemia Associated with Chronic Ulcerative Colitis — As the anemia of this disease is most commonly due to an iron deficiency the therapeutic indication is for the administration of iron as ferrous sulphate in doses of 0 3 to 0 6 gms three times daily following meals Iron therapy is not always successful for two reasons one because in some instances it is said that the patient does not tolerate this form of therapy well and second because the loss of hemoglobin by the bowel may exceed the increased amount which is formed as a result of the iron therapy It has never been my experience that iron has increased the symptoms of chronic ulcerative colitis although other observers have noted this untoward effect I am certain that in some instances such an increase in symptoms has been incorrectly attributed to this factor instead of a spontaneous accentuation in the diarrhea and other complaints If oral iron therapy is not well tolerated intravenous saccharated oxides of iron may be given a trial (see page 96)

If the anemia is of the macrocytic type as shown by a mean corpuscular volume greater than 96 cubic microns then some type of liver extract therapy is indicated and this may be productive of considerable good This should be given in the form of intramuscular injections 1 cc containing 15 units daily or three times a week for the first week and three times weekly thereafter until the blood reaches normal limits or it is decided that the maximum benefit has been attained by this form of therapy Vitamin B_{12} injections may be substituted for the concentrated liver extract and should be just as effective Folic acid may also be helpful

In addition it is advisable to make sure that the patient has an adequate protein intake and that some of this is in the form of milk eggs or lean meat Not only will this be of benefit to the macrocytic anemia but also to the associated deficiency of protein which is not infrequently present as shown by the hypoproteinemia If the proper results are not attained by the use of the measures just described then blood transfusions should be given in a sufficient number to bring the blood to within normal limits Although some have recommended transfusions as small as 100 cc to 250 cc on the grounds that larger ones favor increased bleeding from the bowel this has not been my experience Blood transfusions therefore given to patients have always been in amounts of 500 cc

It has been recommended by some that when these patients have an achlorhydria or hypochlorhydria they should be given dilute hydrochloric acid U S P 4 cc three times daily with meals in a glass of water This is administered on the basis that it favors absorption of iron Such medication has never been productive of benefit in my experience as the amount of hydrochloric acid thus administered is so small in comparison

development of an iron deficiency anemia and the latter through its low content of extrinsic factor may be an important cause of a macrocytic anemia

Fever resulting from the ever present infection in the active cases is also a significant factor in the causation of the anemia because it is thought that infection inhibits the formation of red blood cells as well as the synthesis of hemoglobin

The Severity and Type of Anemia in Patients with Chronic Ulcerative Colitis—In any given case it is difficult to predict from the duration severity and extent of involvement of the gastro intestinal tract whether or not an anemia will be present This is because so many factors may be present to a greater or lesser degree or all may be absent or present to only a slight extent In general it may be said that the longer the disease is present in the active stage the more likely is there to be an anemia *For example it was found by Garvin and Bargen (38)* that those patients with a normal hemoglobin had an average duration of the disease of 1 3 years whereas those with a reduced hemoglobin had an average duration of the disease of three years On the other hand a patient may have a chronic form of the disease persisting for several years with a history that considerable blood has been lost from the bowel and yet a normal red blood cell count and hemoglobin may be present as the result of an adequate diet the absence of an achlorhydria and perhaps only moderate intestinal infection

As previously stated the red blood cell count is not usually reduced below 3 0 million although excessive bleeding from the bowel is known to account for much more severe grades of anemia According to Garvin and Bargen (38) the color index in patients with this disease has a remarkable constancy and is usually in the vicinity of 0 7 This would indicate a moderate type of hypochromia which points to the importance of an impaired intake and absorption of iron and an increased loss of *this element as factors in the causation of the anemia The influence of* a protein deficiency impaired absorption and fever might well tend toward the production of a macrocytic anemia The varying influence of these two groups of causes the one causing a microcytic anemia and the other a macrocytic anemia might act jointly to result in an anemia in which the characteristics were either those of a microcytic normocytic or macrocytic anemia depending upon which group predominated in its effect

The Relation of the Anemia in Patients with Chronic Ulcerative Colitis to the Prognosis and the Indications for Treatment—All evidence indicates that *the presence of an anemia is indicative of a more unfavorable* prognosis It is accepted that there is a parallelism between the severity of the anemia and the relative gravity of the prognosis This is readily understandable as a severe anemia is usually the result of the loss of

more the anemia disappeared when the patient was placed on a liberal diet supplemented by various substances which were known to accelerate the formation of hemoglobin The authors noted that the increase in the amount of hemoglobin occurred despite the persistence of the infection and the loss of blood in the stools

It is their opinion that the deficiency may differ in various cases and hence the anemia is attributable to a number of causes Of great importance is their observation that the response to therapy is not always the same in all patients In some liver extract was effective whereas in a few iron medication had a beneficial effect It must be concluded therefore that some of these patients had a deficiency of the erythrocyte maturing factor now commonly considered to be vitamin B_{12} or that there may have been malabsorption of this material from the intestinal tract or an impairment of the function of the liver in storing it In my opinion it is most likely that there was a deficiency in the intake of vitamin B_{12} which would give rise to a macrocytic anemia resembling pernicious anemia and one which responds favorably to the administration of liver extract

Also it is easy to understand why in some cases there was an anemia of the iron deficiency type which responded favorably to iron therapy This may have been due to a combination of causes as chronic hemorrhage a deficient iron intake infection and an achlorhydria Furthermore in female patients the condition may have been complicated by excessive loss of blood at the time of the menstrual periods or by pregnancy and lactation

The Blood Changes in Brucellosis —Ordinarily there are no striking variations from normal of the blood in this disease In general when a large group of patients with brucellosis are considered there is a tendency for the total average red blood cell count to be approximately 500 000 per cubic millimeter below the accepted normal standards for men and women When a severe grade of anemia is present in patients with brucellosis it is usually due to a complication such as menorrhagia or metrorrhagia a severe secondary infection or some coincidentally associated condition as malaria pronounced malnutrition or some other commonly accepted cause of such an anemia

It is pointed out by Calder and his associates (5) that in this disease there is a tendency toward a macrocytosis with hyperchromia as indicated by an average mean corpuscular volume of 103 9 cubic microns in 30 of their 300 patients and Price Jones measurements which demonstrated that an increased percentage of erythrocytes had a diameter larger than 7 5 microns The *average* mean corpuscular volume however for the entire group of patients was at the higher level of normal as indicated by measurements of 94 3 cubic microns for females and 92 70 for males The mean corpuscular hemoglobin concentration for females was 33.20 per cent and for males 31.20 per cent The changes in size and shape of

to that present in the total amount of gastric juice that in my opinion it could not possibly be of worth while benefit Furthermore if an adequate amount of iron is given it will be absorbed in sufficient quantities to produce satisfactory results without the addition of hydrochloric acid

Anemia in Chronic Bacillary Dysentery —A study of the anemia which occurs in this disease has been made by Keefer, Huang and Yang (39) Their observations have brought to light some of the etiological factors responsible for changes in the blood in this condition The patients observed were all Chinese in the wards of the Peiping Union Medical College Hospital The diagnosis of chronic dysentery was made on the basis of the clinical history including the course of the disease the observation of chronic ulcers in the colon on sigmoidscopic examination and from cultivating dysentery bacilli from the stools To obtain information relating to the kind and prevalence of anemia in this medical clinic Keefer and his associates studied the records of 350 patients They found that anemia was more common in patients with the chronic rather than the acute form of the disease In a study of 16 cases only one had the acute type In these patients the red blood cell count varied from 600 000 to 4 000 000 per cubic millimeter and the hemoglobin from 2 5 to 11 9 grams per 100 cc The color index ranged from 0 6 to 1 25 and the average diameter of the red blood cells from 6 4 to 8 5 microns When the diameter of the erythrocytes was measured and plotted according to the method of Price Jones it was found that three general groups existed cells with an average diameter less than normal cells with a normal diameter and those with a diameter larger than normal In some cases the curve shifted toward the left in others it followed that of normal blood and in others it shifted to the right In some there was a widening of the curve at the base It was observed that cells which had been smaller than normal before treatment approached normal following therapy The same was true of the reaction of the large erythrocytes Hence it may be concluded that in dysentery as observed in China an anemia may be present which may be microcytic normocytic or macrocytic in type and apparently either hypochromic normochromic or of the so called hyperchromic variety

Keefer and his associates (39) considered that the anemia which was present in these patients was apparently due to disturbances in nutrition which were brought about by two principle factors (1) a process which interfered with nutrition (diarrhea and intestinal ulceration) and (2) a faulty diet Other contributory factors such as hemorrhage from the intestine infection or gastric anacidity were of minor importance in their opinion These conclusions are suggested by the fact that all of the patients had chronic diarrhea most of them were partaking of inadequate diets before admission to the hospital and a number had evidences of deficiency diseases such as keratomalacia pellagra and edema Further

when present is usually slight unless it is due to some associated but unrelated condition

Hematologic Changes in Lupus Erythematosus—The most constant finding in the blood of patients with this disorder is a mild to moderate normocytic normochromic anemia although occasionally a hypochromic or hemolytic anemia may be observed It was found by Michael Vural Bassen and Schaefer (40) that in 111 patients with this disease 92 per cent had an anemia as indicated by a hemoglobin of 12 0 or less per 100 cc or 78 per cent of normal The hemoglobin was 11 grams (70 per cent) or less in about 68 per cent of the patients and in 17 patients or 15 per cent of the entire group it was 7 6 grams (50 per cent) or less In several patients it was severe with a hemoglobin as low as 2 5 grams The red blood cell count was 4 1 millions per cubic millimeter or less in 69 patients or 62 1 per cent and 3 0 millions per cubic millimeter or less in 20 patients or 22 per cent

Although it is generally considered that patients with this condition have a *leukopenia* this is not true as only about 60 per cent of this series had a white blood cell count of 5000 per cubic millimeter or less It is of interest to note that these patients are able to respond to a pyogenic infection or an acute spread of the disease with a leukocytosis The differential white blood cell counts showed no constant striking changes There is commonly an increase in the non segmented neutrophils and an occasional patient will have a few (1 to 7 per cent) of myelocytes in the circulating blood Occasionally the lymphocyte quota will be 50 per cent or greater On rare occasions there were a few cells resembling those observed in infectious mononucleosis in the circulating blood or a small increase in plasma cells (1 to 3 per cent)

In about one half of the patients there was a thrombocytopenia of importance (150 000 platelets per cubic millimeter or less) Severe bleeding occurred in only one case but several more had a hemorrhagic rash It should be kept in mind however that a severe thrombocytopenic purpura may be the initial manifestation of the disorder and simulate the idiopathic variety in all respects

The bone marrow was examined in 32 of the 111 patients and in almost all instances the activity of the hematopoietic elements was normal In only one patient was the marrow hyperplastic but later the authors state that two additional patients had a hemolytic anemia with a hyperplastic marrow In general there was no abnormal distribution in the cellular content In 13 cases there was an increase in the plasma cells (over 2 per cent) in one patient it was 18 4 per cent

In general the authors conclude that the hematological picture in systemic lupus is not characteristic The most constant finding is a normocytic normochromic anemia which in more than one half of the cases is associated with a normal white blood cell count and platelet count

the red blood cells, polychromatophilia and other abnormalities of the erythrocytes are rarely encountered in this disease. The reticulocytes are usually within normal limits.

The most common finding which attracts attention is the presence of a normal or diminished white blood cell count in a patient with an obvious chronic infection associated with fever. In about one half of the patients the white blood cell count is within normal limits (6000 to 10 000 per cubic millimeter); in about one third the leukocyte count is below normal, most commonly being between 4000 and 5000 per cubic millimeter but occasionally as low as 2000 or 3000 per cubic millimeter; and in the remaining one sixth there may be a slight leukocytosis. Rarely does the latter exceed 12 000 but occasionally it has been known to reach the vicinity of 14 000 per cubic millimeter.

It is not uncommon to observe a relative and absolute lymphocytosis with an increased number of young lymphocytes present. It was found by Calder, Steen and Baker (5) that 206 (76 per cent) of their 300 patients with brucellosis had more than 30 per cent of lymphocytes in the peripheral blood and 45 (16.6 per cent) had more than 50 per cent. It is thought by the authors just cited that a lymphocytosis is one of the most striking features encountered in the blood of patients with this disease. In their experience it is not rare to observe plasma cells in the circulating blood in numbers varying from 1 to 3 per cent. In general they did not find an increased number of monocytes in the circulating blood and the monocyte-lymphocyte ratio was almost invariably low. In almost all instances it was less than the accepted normal of 0.33 and extremely low values, less than 0.15, were observed in more than one half of the cases. Although the total number of neutrophils was usually reduced, it was frequently noted that the number of immature ("stab") leukocytes was increased above normal. Approximately 20 per cent of the cases showed an eosinophilia of over 5 per cent for which no explanation was obvious.

Other observations made by Calder *et al.* (5) in these patients were as follows: (1) the van den Bergh test on 142 untreated patients showed bilirubin values of less than 0.5 per cent in 87, or 61 per cent. In 55 of the patients (39 per cent), however, the serum bilirubin was greater than 0.5 per cent but in most instances it was less than 1.0 milligrams per 100 cc. of blood.

My own experience with this disease does not indicate that there is a specific blood picture which is of assistance in the diagnosis but the presence of a leukopenia or a normal white blood cell count in a patient with fever always suggests the possibility that the condition may be present. Certainly it is exceedingly rare, just as it is in typhoid fever, to observe an associated leukocytosis unless there is some obvious complication. A severe anemia, it must be agreed, is exceedingly uncommon. An anemia

It should be emphasized that L E cells cannot be found at the time the marrow is aspirated That is in fresh marrow but they may be observed in marrow which stands and to which an anticoagulant has been added The cells may be demonstrated in the peripheral blood and preparations from this source when properly made are as satisfactory diagnostically as those made from bone marrow

Mechanism of Formation of the L E Cell —The exact mechanism resulting in the formation of the L E cell is not known There are at least two factors concerned with the phenomenon first the L E factor of the blood plasma and second, the phagocytic neutrophil which ingests the autolyzed cell It is concluded by Haserick (*49*) who summarizes the previous literature that the gamma globulin of the blood plasma contains the factor which is responsible for producing rosettes of leukocytes and formation of the L E cell in mixtures of normal bone marrow and L E plasma In patients with lupus erythematosus this factor disappears during remissions and reappears in relapses

Further studies by Haserick and Lewis (*50*) show that the factor is an immunologically distinct component of L E gamma globulin It is thought that the L E factor is responsible for the rapid autolysis of neutrophils lymphocytes and megakaryocytes as an initial step in this phenomenon Essential to the process are the polymorphonuclear leukocytes which ingest the autolyzed cells It has been demonstrated that the inclusion bodies in the phagocytes are composed of nuclear material (*42*) According to Holman (*51*) the inclusion bodies in the L E cell and the purple staining masses are nuclear in origin This is substantiated by the fact that they stain with Feulgen s reagent and with methyl green and show a strong absorption at 2537 angstroms (253 7 mμ) all of which indicates that they contain desoxyribose nucleic acid (*52*)

It may be stated that in general the L E phenomenon is a two stage process consisting first of rapid nuclear leukocytic autolysis resulting from the action of the L E factor associated with the gamma globulin of the blood plasma and second the phagocytosis of the autolyzed nuclear material by the intact leukocytes The nature of the material ingested although thought to be nuclear in origin has not been identified with certainty It was believed by Hargraves *et al* (*42*) that it is derived from the nucleus of a polymorphonuclear leukocyte from lymphocytes (*53*) and from megakaryocytes or platelets or collections of amorphous protein (*49*)

It is the belief of Haserick Lewis and Bortz (*49*) that the L E cell is the last step of a two stage process of which the initial stage is the clumping of leukocytes around a blue staining mass By phagocytosis this mass is ingested to form the inclusion bodies characteristic of the L E cell The plasma of patients entering into a remission loses the property of producing L E cells Leukocyte clumping is apparently the last part of the L E phenomenon to disappear with the improvement of the patient (*49*)

A good many patients however, have a leukopenia or thrombocytopenia or both In a few patients the blood may be entirely normal Treatment with ACTH or cortisone did not bring about the degree of improvement observed in the other clinical manifestations of the disorder Their observations concerning the diagnostic significance of L E cells which they consider to be of great importance are given on page 40

The L E Factor and L E Cell—The L E factor is a substance associated with the gamma globulin of the plasma or serum of the circulating blood of patients with lupus erythematosus disseminata which causes the development of the L E cells when plasma or serum is added to cells of the bone marrow or peripheral blood The L E cell is almost always if not always a polymorphonuclear cell which ingests nuclear material platelets lymphocytes or unidentified amorphous material when plasma or serum containing the L E factor is brought in contact with cells from the peripheral blood or the bone marrow

The original observation concerning the presence of L E cells in the bone marrow of patients with acute disseminated lupus erythematosus was reported by Hargraves in 1946 and contained in a thesis by Morton (*41*) Later a preliminary report was made by Hargraves Richmond and Morton (*42*) In this paper they describe the characteristic L E cell as occurring only in the bone marrow of patients with lupus erythematosus The phenomenon was considered to be either a phagocytosis of free nuclear material with a round vacuole containing the partially digested and lysed nucleus or, an actual autolysis of one or more lobes of the nucleus of the involved cell They stated that the L E cell is practically always a mature polymorphonuclear leukocyte They were certain that the L E cell is only the result of a lytic phagocytic phenomenon

In 1948 Haserick and Sundberg (*43*) published a paper corroborating the findings of Hargraves in four acute cases of the disorder and stated that the phenomenon could not be detected in other forms of lupus *erythematosus in dermatomyositis and in other leukopenia conditions* Summaries of information dealing with this phenomenon have been published by Hamburger (*44*) Barnes Moffatt and Weiss (*45*) Berman Axelrod Goodman, and McClaughry (*46*) Beerman (*47*) and Conley (*48*)

In the original description of Hargraves Richmond and Morton (*42*) it is stated that the L E cell is "practically always a mature polymorphonuclear leukocyte In their opinion the chromatin material is in a large phagocytic vacuole and all gradations of digestion of this material is observed In most of the cells the ingested mass is homogenous but some of the chromatin pattern is still thought to be visible The ingested nuclear material varies in appearance from small smoky remnants of digested material to relatively intact nuclei According to these observers actual attempts to phagocytize this free nuclear material may be observed

Technic for Plasma L E Test (i e for demonstrating L E factor)

1 Take $^1/_2$ cc of suspected L E plasma
   a Keep refrigerated to prevent bacterial growth (Bacteria destroy L E factor)
   b If to be sent long distances add powdered penicillin to prevent bacterial growth Do not add merthiolate or benzyl alcohol as these substances are apparently toxic to marrow or peripheral blood cells and like bacteria produce a false negative test
2 Add suspected L E plasma to 1 cc bone marrow or peripheral blood concentrate
   a Bone marrow is placed in paraffin tubes to which powdered heparin has just been added (Hynson Westcott and Dunning heparin such as Lot No 152 is recommended)
   b Whole suspected L E blood may be added to other peripheral blood equal parts mixed for $^1/_2$ hour spun down and the buffy coat examined for the L E phenomenon
3 Allow suspected L E plasma and bone marrow to stand for $^1/_2$ hour *in paraffined tube*
4 Add mixture to Wintrobe hematocrit tube
5 Spin tube at 1000 r p m for five minutes
   a This separates various cell layers and permits white cell layer (buffy coat) to be pipetted off and stained
6 Pipette off buffy coat and smear
7 Stain with Wright s stain
8 Presence of L E phenomenon indicates presence of L E factor in serum tested i e POSITIVE PLASMA L E TEST
   a In human bone marrows look for both rosettes and clumped leukocytes and L E cells
   b In dog marrow L E cells are rare but clumping pronounced
   c Clumping of leukocytes as rosettes is diagnostic more frequently encountered than L E cells

Many modifications of this test have been used The one we have found satisfactory is as follows

SIMPLE TEST FOR "L E" PHENOMENON

This method employs only blood from the patient and does not require use of an anticoagulant

1 Place *2 cc* of venous blood in a serology test tube and allow to stand for *30* minutes at room temperature
2 Rim the clot and pipette off all of the sero sanguineous fluid that can be obtained

The Significance of the L E Cell —In almost all cases of disseminated lupus erythematosus the L E cell may be demonstrated in the films made from the buffy coat of the peripheral blood According to Haserick (*54*) his studies have demonstrated that the plasma L E test has been positive in 23 patients with acute or subacute disseminated lupus erythematosus Furthermore the plasma of one patient with the disease has induced a positive plasma L E test in 46 another in 43 and another in 36 consecutive bone marrow preparations A false negative test was observed in only one patient with the disorder and it was thought that this resulted from a low gamma globulin the test became positive when the patient was treated with cortisone According to this observer the L E test has been negative in the following diseases systemic lupus erythematosus in remission (three of eight cases) chronic discoid lupus erythematosus (eight cases) classic rheumatoid arthritis (13 cases) multiple myeloma (three cases) scleroderma periarteritis nodosa cirrhosis, rheumatic fever dermatomyositis and in 53 miscellaneous disorders Fourteen of the 23 patients with lupus erythematosus disseminata studied by Haserick had no skin eruption at first but six of these later developed typical changes

In a heterogeneous group of more than 700 patients studied by Conley at the Johns Hopkins Hospital (*48*) L E cells were identified in 37 cases in all of which the clinical features were compatible with the diagnosis of disseminated lupus When these cells were demonstrated they usually persisted for months or years Although they may diminish in number following treatment with ACTH or cortisone they rarely disappear It should be emphasized that there is not a strict correlation between the severity of the disease and the finding of typical cells For example the L E cells may be readily demonstrated in asymptomatic lupus and yet they may not be found in some fulminating cases of the disease

Studies in regard to this phenomenon are still in progress Additional important references dealing with various aspects of the phenomena which should be consulted are given (*55 56 57 58 59*)

According to Michael Vural Bassen and Schaefer (*58*) the search for L E cells was of aid in confirming the diagnosis in a number of conditions and should be employed in all patients with unexplained fever leukopenia and thrombopenia and those with hemolytic anemia arthritis nephrosis or uraemia of obscure etiology They have never failed to demonstrate L E cells in the blood or bone marrow in a patient with systemic lupus

It is of interest to note that Walsh and Zimmerman (*59*) have reported the presence of L E" factor in the plasma and L E cells in the bone marrow of three of six patients with severe penicillin reactions They suggest the possibility that the L E phenomenon might be related to hypersensitivity reactions as well as to systemic lupus erythematosus

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Studies in regard to this phenomenon are still in progress. Additional important references dealing with various aspects of the phenomena which should be consulted are given (55, 56, 57, 58, 59).

According to Michael, Vural, Bassen and Schaefer (58) the search for L.E. cells was of aid in confirming the diagnosis in a number of conditions and should be employed in all patients with unexplained fever, leukopenia and thrombopenia and those with hemolytic anemia, arthritis, nephrosis or uraemia of obscure etiology. They have never *failed* to demonstrate L.E. cells in the blood or bone marrow in a patient with systemic lupus.

It is of interest to note that Walsh and Zimmerman (59) have reported the presence of "L.E." factor in the plasma and L.E. cells in the bone marrow of three of six patients with severe penicillin reactions. They suggest the possibility that the L.E. phenomenon might be related to hypersensitivity reactions as well as to systemic lupus erythematosus.

some site in the gastro-intestinal tract or the uterus The most common locations in the gastro-intestinal tract are the stomach or colon particularly the region of the cecum and ascending colon which are known to give rise to the more severe degrees of anemia (*63*) Abnormal uterine bleeding in association with cancer of the cervix is undoubtedly the most frequently encountered cause of anemia due to cancer which is observed in women Rarely is bleeding elsewhere in the body as from the lung or respiratory passages responsible for the anemia of malignancy

2 *Anorexia* An inadequate food intake which is often associated with malignant conditions may account in part for the presence of an anemia This may be due to a deficiency of the protein intake especially with limitation of meat, eggs and milk which we have come to assume is indicative of a diminished intake of vitamin B_1 In some instances also a reduced intake of foods containing iron may contribute to the severity of an iron deficiency anemia although this in itself is probably rarely ever the sole cause of such an anemia A low iron intake however in association with an achlorhydria and chronic hemorrhage may be responsible for a severe iron deficiency type of anemia

3 *Bone marrow metastases* The relation of metastatic lesions to the formation of an anemia has been the subject of considerable discussion for many years Undoubtedly this is usually the main cause of the anemia observed in leukemia and lymphoblastoma of the Hodgkin s type In such conditions the red blood cell forming marrow may in large part be encroached upon or "crowded out" and consequently provide an obvious basis for the presence of a severe anemia which is likely to develop sooner or later in these conditions In other types of malignancy however such as carcinoma of the stomach or the uterus or other varieties of cancer bone marrow metastases is a possible but to me not a very common or important cause of anemia in malignant growths In the opinion of Shen and Homburger (*62*) there is no correlation between bone marrow metastases and anemia in cancer patients It does appear in some cases however that extensive bone marrow metastases may be responsible for an anemia in some patients Three interesting patients with carcinoma of the prostate all of whom had widespread metastases to bone and a severe normocytic normocytromic or slightly macrocytic anemia have been reported by Commons and Strauss (*64*) In two patients no further treatment was given than blood transfusions as this was before the introduction of the present day methods of treating cancer of the prostate The third patient was treated with castration and subsequently with 5 milligrams of diethyl stilbesterol daily after iron and liver extract had failed to control the anemia The orchiectomy and diethyl stilbesterol medication was followed by a return of the blood values to nearly normal where they remained for the period of observation which was 7 months Although the mechanism of the control of the anemia is not clear it is suggested that

3. Place this fluid in a Wintrobe hematocrit tube
4. Centrifuge for 10 minutes at high speed (3000 r p m)
5. Pipette off the clear serum and discard
6. Remove the sedimented material containing red cells and leukocytes with a fine capillary pipette
7. Prepare films on cover slips or slides and stain with Wright s stain as for blood films
8. Search for L E cells with the high dry objective

A simple office procedure has been recommended by Mathis (*60*)

Anemia Associated with Various Other Types of Infections—Almost any type of chronic infection may be responsible for a simple chronic anemia if it is present for a sufficient period of time Among those which should be mentioned are chronic non tuberculous pulmonary infections *such as lung abscess bronchiectasis chronic fusospirochetal infections* especially when associated with repeated hemoptyses and chronic empyema Other conditions as chronic pelvic inflammatory infections osteomyelitis refractory urinary infections of the bladder or those located higher in the urinary tract may also be significant contributing factors to an anemia of this type It is especially true that infection may be important in the causation of an anemia when other significant contributing factors are present such as rapid growth in children and adolescents excessive loss of menstrual blood or bleeding from the gastro intestinal tract achlorhydria which impairs the absorption of iron from the intestines and a diet low in iron

BLOOD CHANGES IN CANCER

From my experience it seems reasonable to estimate that anemia develops in about 75 per cent of all patients with cancer at some time during the course of the disease As is to be expected such a complication is most frequently observed in the more advanced stages but occasionally it may be the presenting symptom which occurs as a relatively early manifestation of the disease In a study of 100 cases of malignancy Morrison (*61*) found that the red blood cell count was slightly decreased in two thirds of the cases markedly reduced in one eighth and normal or increased in one fifth An anemia therefore varying from slight to marked was present in 80 per cent of his patients It was found to be present in 60 1 per cent of the cancer patients observed by Shen and Homburger (*62*)

Causes of Anemia in Cancer—The causes of anemia in neoplastic disease may be enumerated as follows

1 *Acute or chronic hemorrhage* Undoubtedly this is the most common cause of anemia in cancer Furthermore it is responsible for the most severe types of anemia The bleeding almost always occurs from

with the so-called myelopathic anemia other evidences of clinical improvement were not apparent In fact in some the patients were symptomatically worse It is of interest that they do not believe that the presence of metastases to bone usually had no relation to the development of anemia in cancer patients

The Type of Blood Picture—In most instances the blood picture is that of an iron deficiency anemia due mainly to chronic hemorrhage The bleeding is most likely to occur from the stomach or colon sigmoid and rectum or from the uterus Augmenting the iron deficiency thus created is not infrequently a poor iron intake and a deficiency of hydrochloric acid in the gastric juice In such patients the blood picture is one of a micro-

TABLE III

RED BLOOD CELL COUNT AND HEMOGLOBIN PERCENTAGE IN VARIOUS TYPES OF MALIGNANT DISEASE

	Number of Cases	R B C (Millions per Cubic Mm)	Hb (Per Cent)
Cancer Oropharyngeal Cavity	13	4 0	75
Cancer Larynx Epiglottis Thyroid Gland	11	4 0	74
Cancer Lung (Primary)	24	4 0	74
Cancer Esophagus	11	3 9	61
Cancer Rectum	39	3 9	67
Bone Sarcoma	1[illegible]	3 9	69
Cancer Kidney Hypernephroma	1[illegible]	3 7	64
Cancer Ovary	13	3 7	69
Lymphosarcoma	17	3 6	67
Cancer of Colon	18	3 5	63
Hodgkin s Disease	26	3 5	59
Cancer Breast	52	3 4	64
Cancer Biliary Tract	14	3 2	58
Cancer of Stomach	76	3 2	52
Cancer of Uterus	15	3 2	59

(Eisen Courtesy *American Journal of the Medical Sciences*)

cytic hypochromic anemia In the anemia due to bone marrow metastases and the toxic effects of the malignant growth and fever the anemia is of the normocytic normochromic type In the exceedingly rare instances of infiltration of the stomach the anemia may be of the macrocytic variety with a color index of 1 0 or greater and a mean corpuscular hemoglobin concentration of 30 per cent or more

Other Changes in the Blood in Malignancy—In my experience a leukocytosis usually ranging from 12 000 to 20 000 per cubic millimeter with an increase in the polymorphoneutrophils to 75 to 85 per cent or more is commonly observed in patients with cancer at some time during the patients illness According to Morrison (*61*) a leukocytosis occurs in about two thirds of the cases This observer also noted that the leu

the treatment affected the metastatic cancerous material invading the bone marrow thus permitting a more normal formation of erythrocytes If this is true it is an argument supporting the concept that the anemia in prostatic malignancy may be myelophthisic in nature

4 *The presence of fever* which is often observed in all types of malignancy especially when the disease is advanced is also a probable contributing cause of anemia It is known that infection due to microorganisms may be responsible for an anemia as a result of an inhibition of the synthesis of hemoglobin and the depression of erythropoiesis which results from the products elaborated by microorganisms It is logical to assume that the same effect may result from toxic products formed by malignant growths While this is probably true it cannot be said that substantial proof in support of such a statement is available at present

5 *Hypochlorhydria or achlorhydria* may be a condition which favors the production of an iron deficiency anemia due to the impairment of the absorption of iron associated with this condition The diminution or absence of "free hydrochloric acid in patients with malignancy may be due to the cancer itself as in carcinoma of the stomach or the patient may fall into one of the groups of the 5 per cent of the entire population in whom it is estimated that an achlorhydria is present

6 The possibility that the malignant lesion may involve the gastrointestinal function of absorption by the production of a stenosis of the small intestine or colon or serve as the basis of a diarrhea with rapid passage of the intestinal contents through the bowel thereby hindering absorption must be taken into consideration This undoubtedly does occur occasionally but it is probably an infrequent cause of the anemia of malignancy

7 In rare instances it is known as mentioned under the section in the anemia of cancer of the stomach that the intrinsic factor may be destroyed by an extensive malignant infiltration of the stomach and hence produce a macrocytic anemia resembling rather closely the blood picture of pernicious anemia

It was found by Shen and Homburger (62) that the anemia of cancer is due to blood loss alone in 28 5 per cent of the patients to hemolysis in 2 6 per cent to invasion of the bone marrow with metastases or to impaired blood formation in 56 per cent and in 12 9 per cent the anemia was of the myelopathic type just mentioned complicated by blood loss They believe that the etiology of myelopathic anemia in cancer patients and the anemia associated with chronic infection are related Both anemias in their opinion may be due to the inhibition of the bone marrow by toxic products formed by tumor tissue or by the infectious process, or to a disturbance of metabolism of certain amino acids which are required to unite with iron to form hemoglobin Although the administration of cobalt produced some improvement in the blood picture of their patients

with the so called myelopathic anemia other evidences of clinical improvement were not apparent In fact in some the patients were symptomatically worse It is of interest that they do not believe that the presence of metastases to bone usually had no relation to the development of anemia in cancer patients

The Type of Blood Picture—In most instances the blood picture is that of an iron deficiency anemia due mainly to chronic hemorrhage The bleeding is most likely to occur from the stomach or colon sigmoid and rectum or from the uterus Augmenting the iron deficiency thus created is not infrequently a poor iron intake and a deficiency of hydrochloric acid in the gastric juice In such patients the blood picture is one of a microcytic hypochromic anemia In the anemia due to bone marrow metastases and the toxic effects of the malignant growth and fever the anemia is of the normocytic normochromic type In the exceedingly rare instances of infiltration of the stomach the anemia may be of the macrocytic variety with a color index of 1 0 or greater and a mean corpuscular hemoglobin concentration of 30 per cent or more

TABLE III

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kocytosis was associated with an increase in the band forms in 85 per cent of the cases which has likewise been my experience It is well to keep in mind that a *persistent and unexplained leukocytosis may be due to an obscure malignancy* a fact which is sometimes overlooked when the differential diagnosis is considered in a patient who has an increase in the white blood cell count without an obvious explanation Morrison (61) also makes the statement that in over one half of the cases of *leukopenia* which he observed in patients with proven malignancy there were metastatic lesions He considers therefore that the presence of a leukopenia in patients with cancer suggests the possibility that metastases have occurred an observation which I have not had the opportunity to confirm

Other observations made by Morrison (61) with relation to the peripheral blood in patients with various types of malignancy are as follows the bleeding time is only very rarely prolonged and is usually less than one minute The coagulation time is within normal limits The blood platelets are either normal or increased The thrombocytosis according to Morrison is the basis for the non malignant thrombosis seen in patients with malignancy The tourniquet test is rarely positive The fragility test shows no abnormalities The average color indexes accompanying lesions in the various organs were as follows colon 0 57 stomach 0 61, lungs 0 75 breast 0 76 pancreas 0 72 It was found by von Baradulin (65) that in 81 cases of malignancy only one had a color index above 1 0 and three a color index of 1 0

Changes in the Blood in Various Types of Malignant Growths—The average red blood cell count and hemoglobin percentage in various groups of malignant disease are given by Eisen (66) in Table III

It is concluded by Eisen (66) that the outstanding feature of the blood in cancer is the tendency of the anemia to become more severe as the neoplastic process progresses This is not uniformly true however for it is known that the anemia does not always reflect the general condition of the patient Some patients have only a moderate anemia throughout the course of the disease while others present a severe stage apparently out of proportion to the early development of the neoplasm It is emphasized by Eisen that the most severe anemia is associated with cancer of the stomach and especially in those patients with excessive hemorrhage and in whom there has been a striking loss of weight It should be pointed out also that an anemia of almost equal severity was present in patients with cancer of the uterus in which it is probable that the anemia is largely due to hemorrhage alone

Such data as given by Eisen can only give an approximate idea of the severity of the anemia in any given group of patients with cancer as the degree depends so often upon the stage of the disease in which the blood is examined At the present time when the diagnosis of malignancy is made at a much earlier date than in previous years it is not likely that

anemia of a severe grade will be so commonly present when the condition is first recognized but that it will develop during the time the patient is kept under continued observation

The average white blood cell count in the group of cases of malignancy studied by Eisen (66) was found to be 10 000 per cubic millimeter with an average of 71 per cent polymorphonuclear leukocytes Sixty per cent of his cases had a normal white blood cell count and 36 per cent a leukocytosis and 4 per cent a leukopenia In his opinion it is doubtful if un*complicated cancer has the power to increase the number of leukocytes* in the blood He believes that the very high white blood cell counts are invariably attributable to a complication It should be kept in mind however that a persistently elevated white blood cell count in an adult may have as its basis a malignant process of an obscure nature in the body

Changes in the Blood Due to the Therapeutic Use of the Roentgen Ray in Patients with Cancer—It is the opinion of Eisen (66) that radio*therapy does not increase the severity of anemia It appears possible that* the roentgen ray radium and the more recently employed radioactive elements may cause an anemia or increase the severity of such a blood condition when it is already present Such an effect however does not develop immediately after the irradiation but is delayed until six to eight weeks after exposure As relatively large doses of these therapeutic agents are often administered it is likely in my opinion that they may *contribute substantially to the anemia which is present in various types of* malignant growths

Anemia in Cancer of the Stomach—Cancer involving the stomach is the most common of all types of malignancy in the body and hence ranks high among the common causes of death As it occurs most frequently after the age of 35 years and longevity is increasing at a remarkable rate in this country the number of persons attaining the age when cancer is prevalent is increasing Hence it is to be anticipated that the incidence of cancer of the stomach with its associated anemia is likely to be greater in the near future years

The incidence of anemia in patients with this type of malignancy is high provided a sufficient number of observations on the blood of such patients are made over a long period of time In fact it may be said with considerable assurance that an anemia will develop eventually in almost all such patients at some time during the course of the illness If the blood is examined over short intervals in patients in all stages of the disease however an anemia will be present in only about 75 per cent of the patients Usually this is not pronounced as often the hemoglobin is in the vicinity of 75 per cent (67)

Undoubtedly the principle cause of the anemia of gastric cancer is an iron deficiency which is mainly due to chronic hemorrhage and less frequently to the acute loss of relatively large amounts of blood Other

with the normal rate of production of red blood cells Although this is recognized as a possible cause of anemia in malignant growths it is certainly not a common one in my experience

Treatment of the Anemia of Cancer of the Stomach—It is emphasized by Heath (69) that too often a patient with inoperable carcinoma of the stomach is regarded as a hopeless problem, and after surgical possibilities are exhausted the treatment is limited solely to the mitigation of pain by means of opiates He points out that often the associated anemia may be alleviated at least in part by suitable medication, and a trial of such therapy is always worth while According to this observer the most common type of anemia in carcinoma of the stomach is the iron deficiency variety which is attributable to the loss of blood an inadequate diet as a result of the commonly associated anorexia poor in hemoglobin building substances notably iron and the presence of an achlorhydria which lowers the hydrogen iron concentration in the upper intestine and prevents the maximal absorption of iron from the digested food Although *patients with advanced carcinoma of the stomach may not respond to the* administration of this metal at the usual rate of 1 per cent of hemoglobin per day the trial of such medication is indicated in his opinion in all cases in which there is evidence of an iron deficiency anemia

It is emphasized by Heath (69) that cancer of the stomach may in some instances occur in patients with pernicious anemia In such patients improvement in the blood condition may follow the administration of liver extract intramuscularly He suggests that the color index is the most valuable simple aid in differentiating between the types of anemia In his opinion the anemia in carcinoma of the stomach associated with the toxic effects of the carcinoma and that due to bone marrow metastases cannot be alleviated by any form of medication

In my own opinion there are three palliative therapeutic possibilities any one of which may be well worth while in such a condition These are *the administration of iron in adequate doses the parenteral injection of* liver extract or vitamin B_1 and the judicious employment of blood transfusions The main objective as I see it in treating the anemia of gastric *cancer is to make the patient more comfortable* and not necessarily to prolong his life In Figure ▮ is shown the remarkable effect of the administration of a simple preparation of iron to a patient with carcinoma of the stomach This added materially to the patient s comfort by increasing his strength and permitting him to be more active and attend to his business affairs for a considerable period of time As a great majority of patients with cancer of the stomach ultimately develop an iron deficiency, *it is advisable in my opinion* to begin the administration of iron in the form of enteric coated ferrous sulphate tablets 0 3 to 0 6 grams (5 to 10 grains) three times daily, as soon as the diagnosis is established If then an anemia of a macrocytic type should develop a potent liver extract such

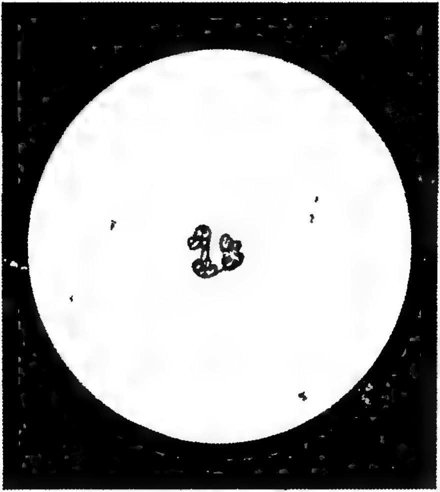

PLATE I *Microcytic Hypochromic Anemia*—The erythrocytes are poorly filled with hemoglobin and vary considerably in size and shape Diffuse and punctate basophilia is present and elongated cigar shaped red blood cells are se Although there is a tendency to microcytosis with a mean corpuscular volume of 78 cubic microns the most characteristic quantitative abnormality is the reduction of the mean corpuscular hemoglobin concentration to a value of 24 per cent In this patient the anemia was of relatively short duration induced by repeated severe hemorrhages from a peptic ulcer In long standing cases of iron deficiency whether due to chronic blood loss or other causes microcytosis may be extreme Wright s stain Magnification 960

as used in the treatment of pernicious anemia should be given in doses of 1 cc (15 units U S P) intramuscularly three times weekly until the blood is normal and once weekly thereafter or an equivalent dosage of vitamin B_1 may be given parenterally Furthermore an attempt should be made to have the patient partake of at least one quart of milk one egg and a serving of meat daily which will supply an adequate amount of the extrinsic factor If these measures fail to maintain the level of the blood at a point where the symptoms of anemia are absent then a sufficient number of blood transfusions should be given to maintain the blood at a level of at least 11 0 grams of hemoglobin per 100 cc of blood

ANEMIA DUE TO IMPAIRED RENAL FUNCTION

Etiology —It has long been recognized that anemia commonly develops in patients with chronic glomerular tubular nephritis although its cause *even at the present time* is not settled Ceconi (70) in 1905 was the first to suggest that it was probably due to the action of retained toxins which caused a deficiency of the hematopoietic system Grawitz (71) was of the opinion that the anemia might result from an increase in the water content of the blood plasma but this was disproven by the work of Keith Rowntree and Geraghty (72)

There is no indication that blood loss as indicated by the hematuria in these cases ordinarily plays a significant etiological role This was shown by the observations of Brown and Roth (73) (74) who found that in 89 cases of chronic nephritis with anemia 34 or 38 per cent of the patients showed no erythrocytes in the urine although the hemoglobin of the circulating blood averaged 59 per cent and the red blood cells 3 01 millions per cubic millimeter Furthermore they observed that there was no relationship between the amount of blood in the urine if cases of gross hematuria were excluded and the degree of anemia For example in four cases in which there were many red blood cells in the urine the hemoglobin of the circulating blood was 57 per cent and the erythrocyte count 2 95 millions per cubic millimeter whereas in those patients in whom they were almost entirely absent the hemoglobin averaged 54 7 per cent and the red blood cell count 3 31 millions per cubic millimeter

MacArthur (75) concludes that in children with chronic hemorrhagic nephritis there is often a severe normocytic normochromic anemia in association with a normal or slightly increased number of reticulocytes and a mild leukocytosis This author points out that its etiology is difficult to explain The blood picture is not that of an aplastic anemia nor is there any evidence that the condition is due to loss of blood through the kidney The amount of blood in the urine is small and furthermore if blood loss were the responsible etiologic agent, it would lead to a hypochromic anemia *unlike* the true anemia of nephritis and would be responsive to iron therapy Against the idea that the anemia is associated with

aplasia of the red blood cell forming marrow is the fact that neither the white blood cells or reticulocytes are reduced in numbers According to MacArthur there is no treatment which will influence this form of anemia

The most generally accepted theory has been that it results from a depressed hematopoietic activity of the red blood cell forming elements in the bone marrow which in some unknown manner is secondary to severe impairment of renal function More recently it has been pointed out by Emerson (76) that the evidence in support of this explanation is large based on inference and exclusion and that there are few positive findings in surpport of it After a careful study of one case with acute glomerulonephritis in an attempt to determine the mechanism of production of the anemia he concluded that the responsible factors were increased blood destruction and impairment of blood formation A review of the previous articles dealing with this subject is given

It is reported by Nordenson (77) that sternal puncture in a group of cases of chronic nephritis studied by him showed a diminution in the number of cells belonging to the erythropoietic system He did not regard this diminution however to be of such an extent that he could speak of it as a genuine aplasia He did however conclude that the anemia in chronic nephritis is conditioned by reduced bone marrow function due to an "incipient aplasia" of the red blood cell forming tissues He suggested that the cause of this aplasia is not quite clear but that several factors may play a role in it the most likely being the diminished renal function and the duration of the nephritis A majority of observers consider that the anemia of nephritis is probably due to diminished blood production There is no general agreement however that a basis for this has been found by the demonstration of an aplastic bone marrow Furthermore it must be kept in mind that hemolysis may play a role in some cases

All observers who have studied the problem in humans recently are in agreement with the statement that the anemia is related to an inability of the body to eliminate nitrogen or at least all are in accord with the observation that when an anemia of this nature is present there is almost always nitrogen retention This may be due to nephritis congenital polycystic kidneys conronic prostatic obstruction and the functional failure of the remaining kidney when the other has been removed surgically Although information on this question is not adequate it appears that the anemia does not develop until changes in the urinary system have been present for some time There is no evidence to indicate that acute supression of urine due to the inactivity of the kidneys may cause an anemia

The observations of Townsend Massie and Lyons (78) have thrown new light on the underlying cause of the anemia associated with nitrogen retention and their studies deserve the careful consideration of all those are in this question These authors confirmed the con workers that the anemia becomes manifest as the

renal insufficiency occurs and is increased in proportion to the degree of nitrogen retention. They base their theory on the fact that in nephritis there is a pathologic condition which prevents the normal elimination of the end products of protein metabolism and the normal regulation of the acid base equilibrium especially in the chronic active and terminal stages of the disease. When there is sufficient renal impairment to cause nitrogen retention there is also an associated disturbance in the acid base control of the body and hence a degree of acidosis is developed which varies with the amount of nitrogen retention. As the condition progress the nitrogen retention becomes increased and a striking acidosis develops as indicated by a decrease in the carbon dioxide combining power of the blood plasma. With this there is an associated diminution in the gastric acidity. When the carbon dioxide combining power reaches 30 volumes or less there is complete gastric anacidity even following the use of histamine.

To these observers one of the most important features in the anemia of glomerular nephritis is the diminished or absent HCL in the gastric secretion which they assume results in impaired digestive processes and improper absorption of food and iron. These abnormalities they believe are the causes of a deficiency of "building material" for sufficient red blood cell formation and the production of hemoglobin. They regard this as an important factor in the continuance of the condition and as one of the possible explanations for the lack of response to therapy. In my opinion the diminished hydrochloric acid probably does not play a major role in the production of the anemia although it may contribute to it. Too many normal persons have an anacidity with a perfectly normal blood to suggest that the impaired gastric function is the chief cause of the anemia in nephritis. On the other hand the authors point out the important fact that these patients with nitrogen retention also have a chronic acidosis with a carbon dioxide combining power which is often below 40 volumes per cent and in some instances less than 20 volumes per cent. *The possibility that the anemia may be attributable to a chronic acidosis which operates in some unknown manner* must be given serious consideration and should be investigated further.

There have been some recent experimental studies on the problem of anemia in nephritis which are of interest but they have not been especially helpful in establishing the cause of the anemia. In a study of the hemoglobin production in dogs who developed nephritis spontaneously Whipple and Robscheit Robbins (79) found that the animals retained only about two thirds of their normal capacity to form hemoglobin in the last year of life. In their opinion this did not indicate an impairment which would give rise to an anemia in such animals. During the last month or two of life however when the non protein nitrogen was high and the dog was on the verge of uremia the hemoglobin production was

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at the present time except blood transfusions The severity of the anemia varies directly with the degree and duration of nitrogen retention and as at present we have no effective way of dealing with this condition it is not to be expected that the anemia can be successfully combatted Repeated blood transfusions may be tried (81), and some have reported that they have benefited the patient in a worth while way, and in my experience they have been of considerable value As the anemia is always associated with evidence of renal insufficiency and nitrogen retention it is always of grave significance and portends an ominous outlook

Recently Gardner (82) has reported that the anemia in patients with chronic renal disease and an elevated blood urea nitrogen can be benefited by the oral administration of cobaltous chloride in a total daily dose of 50 to 100 milligrams given with meals If the dose exceeds 100 milligrams nausea and vomiting may appear Other toxic manifestations were occasional diarrhea and transient tinnitus and deafness In his opinion after treating 17 patients the administration of this drug stimulated erythropoiesis and caused a worth while increase in the hemoglobin and red blood cell count in patients with uraemia after 4 weeks of treatment

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observed to fall to zero in some cases but again in other animals it was only slightly impaired They concluded that nephritis causes little or no change in the hemoglobin production in anemic dogs in the early stages of the disease In the late stages of nephritis there may be no change or moderate changes in the hemoglobin production in advanced nephritis It is their belief that an impairment of hemoglobin formation of this extent would not cause an anemia in the dog It is possible that in dogs a study of the development of an acidosis might correlate the findings in these animals with nephritis and anemia in humans

Changes in the Blood in Nephritis —The figures in the literature relating to anemia in patients with nephritis and nitrogen retention have been collected by Parsons and Ekola Strolberg (*80*) These indicate that there is a definite anemia in practically all patients with azotemia The red blood cell count usually averages about 3 0 millions per cubic millimeter and the hemoglobin between 50 and 55 per cent (8 25 to 9 0 grams) In the group studied by Townsend Massie and Lyons (*78*) the mean corpuscular volume averaged 88 cubic microns the mean corpuscular hemoglobin 28 micrograms and the mean corpuscular hemoglobin concentration 31 per cent It can be said therefore that the average patient with the anemia associated with nitrogen retention has a normocytic normochromic anemia It should be emphasized however that in some patients the mean corpuscular hemoglobin concentration may be below 30 per cent which would indicate a hypochromic type of anemia

Usually there is but little anisocytosis and poikilocytosis and immature red blood cells as indicated by nucleated erythrocytes and those with reticulum and polychromatophilia are not commonly observed in the circulating blood Reticulocytes in a percentage of 1 2 have been noted in the peripheral blood by Emerson (*76*)

The white blood cell count was found to be slightly elevated by Parsons and Ekola Strolberg (*80*) averaging 13 839 per cubic millimeter but Brown and Roth (*73*) found an average of only 9020 per cubic millimeter In uncomplicated nephritis with an anemia there is little or no shift of the leukocytes but with an infection such as sinusitis tonsillitis or otitis media there is a leukocytosis with a shift to the left in the neutrophils

Although Brown and Roth found a reduction in the number of blood platelets with counts which averaged 152 000 per cubic millimeter this has not been the experience of other observers Parsons and Ekola Strolberg (*80*) did not find a material reduction in their cases and this is in accord with my observations Any bleeding tendency with the production of purpura in patients with chronic glomerular tubular nephritis is usually considered to be due to an increased permeability of the capillaries of the vascular system

Treatment —The anemia of nephritis is not amenable to treatment with iron liver stomach preparations or any other form of therapy known

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CHAPTER III

IRON DEFICIENCY ANEMIA

(Hypochromic Microcytic Anemia)

Definition.—A commonly encountered hypochromic microcytic type of anemia which results from an inadequate supply of available iron in the body for the formation of the normal amount of hemoglobin. Such a deficiency is most commonly due to chronic hemorrhage which occurs with the greatest frequency from the gastrointestinal tract in males and from the uterus in females. Other causes of a subnormal amount of iron in the body which may contribute to the etiology of such an anemia are a low dietary intake, malabsorption from the gastro-intestinal tract, an increased demand for the metal or any form of infection which may inhibit its utilization. Regardless of the cause, a gratifying response usually follows the therapeutic administration of iron in the proper doses.

It is now recognized that the nutritional anemia of infancy and childhood, chlorosis or the hypochromic anemia of adolescent girls, the hypochromic anemia of pregnancy and of chronic blood loss, and idiopathic hypochromic anemia of adult women are all varieties of the same condition which results from a deficiency of available iron in the body. These clinical syndromes have much in common. They differ chiefly because of the age and sex of those affected.

History.—The story of the development of our knowledge of the iron deficiency anemias and the therapeutic use of iron is a fascinating one which dates from early Greek civilization. It is an amazing fact that this metal was introduced as a therapeutic agent as a result of the simple association of the idea in the minds of men that iron meant strength and protection, and hence they argued it undoubtedly would be of value in the treatment of persons who suffered from weakness regardless of its cause. This is an excellent example of how a wholly incorrect and naive premise may serve as a basis for the introduction of new and valuable additions to our medical knowledge.

The initial basis for the introduction of iron into medicine is well described by Christian (*1*) who says, "The pantheistic Greek of this early period gave expression to the idea that Mars in some subtle way had imbued iron with force and properties which they did not regard as inherent in the metal itself but thought that the metal acted merely as a vehicle for the transmission of divine power. In this way they believe

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He advocated the simplest forms of iron and says "Next to steel in substance I prefer a syrup. This is made by steeping iron or steel filings in cold Rhenish wine. When the wine is sufficiently impregnated strain the liquor, add sugar, boil to the consistency of a syrup." He furthermore holds that natural iron waters are simply "waters except so far as they are impregnated by the minerals through which they pass. This will be clear if we only throw some horseshoe nails in a few gallons of common water. By afterwards adding powder of galls, tea leaves or the like we shall find the colour is just that of mineral waters of the same mixture ... the artificial waters have the same effect with the inartificial or natural—call them what you will." There can be no doubt but what Sydenham obtained results from his iron therapy, for he certainly must have given, if only by chance, iron to some patients who had an iron deficiency, and the doses which he advocated, from 0.5 to 1.0 grams of iron filings daily, were sufficiently large to produce the described effects.

It is probable that Francis Hoffman (5) first gave an accurate and complete clinical description of chlorosis in his *Dissertatio de Genuina Chlorosis Indole, Origine et Curatione* published in 1731.

In 1836 Ashwell (6) published a paper of 50 pages in which he presents his *Observations on Chlorosis and its Complications* and incorporates 15 illustrative case histories. In this report he emphasizes that the disease is "a peculiar affection of the general health ... invariably connected with either an entire absence of menstruation or with imperfection and irregularity of the function ... a disease essentially characterized by anemia of the system and pallor of the surface." He enthusiastically advocates the early use of iron in the form of ferrous carbonate and iodide of iron in large doses.

The development of our knowledge concerning the actual changes in the blood in chlorosis came slowly with the methods of the microscopic examination of blood. In 1661 Thomas Willis made the observation that in patients with this disease the blood was watery (7). Lemery and Geoffry in 1713 (8) demonstrated the presence of iron in the ash of the blood, but it was not until 1832 that Fodisch discovered that the blood of such patients was deficient in this material (9).

The observation that the depth of color of the blood in patients with this disease was lighter than in normal persons had been made by Hoefer (*10*) in 1840 and five years later Popp (*11*) noted that the individual corpuscles were of a paler color. Duncan made some remarkably accurate studies on the blood in 1867 (*12*) in which he observed that the depth of color of the blood in patients with this malady was not as great, but that the red blood cell count was approximately normal. Thus he indicated correctly that the anemia was one in which the color index was low and the deficiency was therefore in the hemoglobin rather than the red blood cells.

that iron possessed a curative force for injuries received in war. This superstition held for many years and the early pharmacopoeias spoke of iron as Mars and we find crocus martis, saffron of Mars, tincture of the syrup of Mars with tartar.

The therapeutic use of iron is closely linked with the disease chlorosis because it was in this condition that prompt and dramatic results were first achieved by the use of iron preparations. Although there may have been some vague references to chlorosis in the writings of Hippocrates and other contemporary writers, credit for the first description of the disease must be given to Johannes Lange (1485–1565) in the Epistola XXI entitled *De Morbo Virgineo* found in his Medicinalium epistolarum miscellanea (2). *In this publication he refers to a young girl who is* exsanguinated, sadly paled, the heart trembles with every movement of her body, and the arteries of her temple pulsate, and she is seized with dyspnea in dancing and in climbing stairs; her stomach loathes food and particularly meat, and the legs especially at the ankles become edematous at night. He refers to Hippocrates as advocating venesection to cure the condition. Lange makes the statement that pregnancy is of benefit in eliminating the disease: if they conceive they recover. This is hardly in accord with our modern view that young women who have an iron deficiency anemia often become very much worse during pregnancy.

In the sixteenth and seventeenth centuries the condition was separated as a distinct clinical entity but as modern clinical laboratory methods were not then available, various types of anemia other than that due to a deficiency of iron were undoubtedly included in the group. According to Allbutt (3) the name chlorosis was given to the condition by Jean Varandal in 1620. It is derived from the Greek word meaning "green" and the name "green sickness" was commonly used for chlorosis by Sydenham and other contemporary writers.

To Thomas Sydenham (1624–1689), the great English clinician (4), must be accorded the credit for having popularized the use of iron with which he undoubtedly obtained good therapeutic results although he had no scientific basis for administering it. He advocated its use in chlorosis, a truly hysterical complaint. In describing his treatment for this condition he says: "I comfort the blood and the spirits belonging to it by giving a chalybeate 30 days running. This is sure to do good. To the worn out and languid blood it gives a spur of fillip whereby the animal spirits which before lay prostrate and sunken under their own weight are raised and excited. Clear proof of this is to be found in the effects of steel upon chlorosis. The pulse gains strength and frequency, the surface warm, the face (no longer pale and deathlike) a fresh ruddy color. Here however I must remark that with weak and worn out patients the bleeding and purging may be omitted and the steel be begun with at once."

He advocated the simplest forms of iron and says "Next to steel in substance I prefer a syrup. This is made by steeping iron or steel filings in cold Rhenish wine. When the wine is sufficiently impregnated, strain the liquor, add sugar, boil to the consistency of a syrup." He furthermore holds that natural iron waters are simply waters except so far as they are impregnated by the minerals through which they pass. "This will be clear if we only throw some horseshoe nails in a few gallons of common water. By afterwards adding powder of galls, tea leaves or the like, we shall find the colour is just that of mineral waters of the same mixture ... the artificial waters have the same effect with the inartificial or natural—call them what you will." There can be no doubt but what Sydenham obtained results from his iron therapy for he certainly must have given, if only by chance, iron to some patients who had an iron deficiency and the doses which he advocated, from 0.5 to 1.0 grams of iron filings daily, were sufficiently large to produce the described effects.

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All authorities agree that it was Hayem (*13*) who by his accurate hematological observations placed the disease chlorosis on a firm foundation in 1889. He demonstrated that the erythrocytes in the disease average 6.5 to 6 microns in diameter as compared to the normal of 7.5 microns and that the amount of hemoglobin per corpuscle was diminished in the disease.

It was Pierre Blaud (*11*) who recognized the fact that the condition arose from the faulty formation of blood and that iron possessed the property of restoring the blood to normal. To Blaud must be accorded two exceedingly important aspects of iron therapy, namely, the administration of a ferrous salt which in later years has been shown to be more readily absorbed, and the insistence that large doses should be given. His original prescription which consisted of equal parts of ferrous sulphate and potassium carbonate combined with the aid of mucilage of tragacanth contained the equivalent of 5 grains (0.3 gm.) of ferrous sulphate or approximately 2 grains (0.12 gm.) of ferrous carbonate in each pill. The principles of iron therapy laid down by Blaud were accepted and followed for years by such eminent clinicians as Felix von Niemeyer whose textbook was the standard in Germany for many years, and by Immermann who was the editor of the Cyclopedia of Practical Medicine.

In the first edition of Osler's famous textbook published in November 1891, a very excellent resume of what is known at that time concerning chlorosis is given. The use of iron is warmly advocated. He says "I have for years, in the treatment of chlorosis, used with the greatest success Blaud's pills made according to the formula in Niemeyer's textbook, in which each pill contains 2 grains of the sulphate of iron." When used in accordance with Osler's plan of therapy, the patient would receive 6 grains of ferrous sulphate daily for the first week, 12 grains daily for the second week, and 18 grains daily during the third week. The latter dose was continued for four to five weeks before reduction. He then adds "the important feature in the treatment of chlorosis is to persist in the use of the iron for at least three months, and if necessary, subsequently to resume it in smaller doses, as recurrences are so common."

It has now been firmly established that iron has a specific action when the proper dosage is given to patients with an iron deficiency anemia. Its wide acceptance, however, did not come without strong opposition at intervals. Over the course of years the value of the metal had been firmly established in the treatment of chlorosis only to have the efficacy of the drug challenged seriously by Gustav Bunge (*15*). This investigator's dogmatism and personal prestige was responsible for the curious controversy that iron was not useful in the practice of medicine because science had found a reason in the laboratory why this should not be so. The amazing apparent conflict between what the clinician has actually noted accurately in hundreds of patients and an observation in the experimental

laboratory which was thought to be incompatible with this has more than once been observed in medicine. The most remarkable aspect of such a conflict is how often the laboratory achieves a temporary victory which is subsequently reversed completely. Such a sequence of events occurred in the difference of opinion concerning the use of iron in the treatment of anemia. In 1895 Bunge (*15*) promulgated the idea that inorganic iron could not be absorbed from the intestinal tract because it was converted into the sulfide and hence could not possibly be of value in the treatment of anemia. This erroneous statement carried great weight in the scientific world and also among clinicians and hence had its unfavorable influence for many years on the use of this valuable drug. These beliefs persisted despite the evidence accumulated by Stockman (*16*) that the views held by Bunge were erroneous.

Nevertheless it was Bunge who must be considered the father of the present conception of an iron deficiency as a basis of certain types of anemia. It was he and Abderhalden (*17*) who demonstrated that lactating animals store relatively large amounts of iron during the latter period of gestation and that this reserve thus created is gradually utilized during lactation and when this is prolonged for a sufficient period of time an anemia will result.

It is also undoubtedly true that small and therefore ineffective doses of iron were introduced as a result of the opinions of Quincke (*18*) and of von Noorden (*19*) who believed that only 0.1 gram (1½ grains) daily of metallic iron was necessary in the treatment of chlorosis. These views although incorrect from a therapeutic standpoint were understandable because it was known that the body utilized only a few milligrams of iron daily.

There can be no question about the ability of Immermann in 1877 (*20*) to achieve the proper results in chlorosis with iron. He gives the following definite advice which is as highly satisfactory today as when it was given, as follows: "... large doses of the remedy (iron) cures the disease far more certainly and quickly than small ones. Whether large or small doses be given the quantity of iron which is absorbed is insignificant, this is clear from the black color of the feces after a considerable dose, due as it is to the formation of insoluble iron sulphide in the bowel. Nevertheless ... the administration of small doses recommended by some writers on theoretical grounds has never become popular and my own very numerous observations have convinced me of the immense superiority of large doses in the treatment of true uncomplicated chlorosis. ... I need only to add that I agree with Niemeyer in thinking the dose of more importance than the compound selected."

An excellent historical review of the development of our knowledge concerning the therapeutic use of iron containing many references has been written by Herbert (*21*).

When I was a student and until the year 1918 when Lichtenstein (22) reintroduced large doses of iron the metal was never observed to accomplish much good in patients with anemia and I was in a quandary to understand why the older clinicians had held the drug in such high esteem Undoubtedly the skepticism in my early medical experience toward the effectiveness of iron was due to the following four reasons (1) the diminution in the number of cases of true chlorosis (2) iron was employed in many conditions in which there was not an iron deficiency such as pernicious anemia and leukemia in which it could not possibly accomplish good (3) it was also used following acute hemorrhage in persons who had previously been healthy and in whom the iron reserves were intact hence the blood would regenerate as rapidly without the administration of therapeutic iron as with it, (4) because iron was administered in suboptimal doses

The highly important matter of whom to recognize as responsible for the re establishment of adequate doses of iron is difficult to determine In 1925 Arneth (23) recalled that he had advocated large doses of reduced iron (from 0 75 to 0 9 grams daily) twenty years before and his views concerning this are given in his textbook which was published in 1907 Meulengracht (24) published an article in 1923 suggesting large doses of iron in various types of anemia and it was his work which brought the attention of the medical world once again to the importance of large doses of the metal Well do I remember shortly after its appearance that Dr George Minot referred me to this publication with the information that Meulengracht had observed success with exceedingly large doses of iron in certain types of anemia Before the publication of Meulengracht it had been stated by Lindberg (25) that the administration of iron in doses greater than ordinarily used was effective in the treatment of the anemia which followed influenza infections

ETIOLOGY

Frequency —These anemias are of the greatest importance because they are among the most commonly encountered ones in clinical medicine throughout the world and because they usually respond satisfactorily to the administration of iron As an indication of their frequency the figures of Davidson Fullerton and Campbell (26) may be cited they examined the blood of 3500 persons representing a cross section of the poor of Aberdeen Scotland, and found an iron deficiency anemia to be present in 41 per cent of the infants under the age of 2 years in 32 per cent of children of preschool age, 16 per cent of adolescent girls and 45 per cent of adult women Mackay *et al* report (27) that two thirds of the hospital class of London have such an anemia and Patek and Heath (28) found that it was present in 16 per cent of the women admitted to the wards of the Boston City Hospital

Evidence which has been accumulated recently indicates that anemia is probably more frequently encountered in the United States than had previously been suspected and that the iron deficiency variety is one of the most common types. For example, from observations made at the University Hospital, Ann Arbor, Michigan, in 1942 and 1943 (29) on all patients 14 years of age or older who came to the in-patient and out-patient departments showed that 12.4 per cent had an anemia. This percentage was based upon the routine study of slightly over 11,000 patients in whom the lower limit of normal for hemoglobin in the circulating blood of males was set at 86 per cent (13.4 grams per 100 cc. of blood) and for adult females 78 per cent (12.2 grams per 100 cc. of blood). Levels below these arbitrarily selected limits of normal were regarded as representing anemias which were clinically significant. Of the group who had an anemia, it was found that 41 per cent were of the iron deficiency variety, and of these 16.8 per cent were mild and 24.2 per cent were moderate or severe in degree.

McIntosh and Morris (30) carried out hematologic studies on over 1000 residents of Glasgow, Scotland, who were receiving public assistance and observed that hypochromic anemia was prevalent in children under four years of age and in women during the reproductive period of life. The incidence was low in school children and in men and in women over 50 years of age. Pregnancy, childbirth, lactation, and to a less extent menorrhagia were considered important etiologic factors in women. Of 364 college women examined by Pryor and Ferguson (31), 145 had hemoglobin levels below what they considered to be normal. A study of the incidence of hypochromic anemia in private patients was reported by Bunce and his associates (32) in which they found that 38 per cent had this condition. The ratio of females to males in their patients was 4:1. They considered the chronic loss of blood, poor diet, gastric anacidity, hypothyroidism, pregnancy, and chronic infections as important in causing the anemia. Heath (33) states that a mild anemia apparently of the hypochromic type was present in about one fourth of the girls entering the nursing service at the Boston City Hospital.

The Metabolism of Iron.—Iron Content of the Body.—As pointed out by Hynes (34), if an average man has a blood volume of 6 liters with a hemoglobin content of 15.5 grams per 100 cc., his total circulating hemoglobin would be 930 grams. If the average life of the red blood cells is 120 days, the daily breakdown of hemoglobin would be 930/120 or 7.75 grams which contains 26 milligrams of iron, as 1 gram of hemoglobin contains 3.4 milligrams of iron.

According to Granick (35), if the total body iron is assumed to be 4.5 grams, 60 to 70 per cent will be contained in the blood hemoglobin, 3 to 5 per cent in the muscle hemoglobin (myoglobin), 0.1 per cent in the heme enzyme (cytochrome C), 0.1 per cent plasma iron (siderophilin),

and 15 per cent ferritin the normal iron storage protein of the body

The Iron Reserve of the Body—It is known that a healthy adult may lose one third of his total circulating red blood cells and provided the *source of bleeding is controlled* the hemoglobin will regenerate at the rate of about 1 per cent daily until it reaches normal without the administration of therapeutic iron This is accomplished by utilization of the iron reserves chiefly available from the stores in the liver spleen and bone marrow It is estimated by Hynes (*34*) that a normal man has an available iron reserve of about 650 milligrams which is sufficient to regenerate approximately 1700 cc of blood or about one third of the entire blood volume

Daily Iron Requirements—The normal body requirements for iron plus a sufficient quantity to create and maintain reserves should be the *normal dietary intake of iron If the figures of Hawkins and Hahn (36)* for the dog can be taken for man it is estimated that 0 8 milligram is lost in the stools largely as a result of excretion into the bile A smaller amount 0 4 milligram per day is excreted in the urine If there is no loss of blood the daily requirements for the healthy adult male would then equal the sum of these or 1 2 milligrams The needs of women in the period of reproductive life are greater however due to the loss of iron in the menstrual blood According to McCance and Widdowson (*37*) the normal woman loses between 10 and 30 milligrams of iron in each menstrual period and hence the total maximum loss may be given approximately as about 1 milligram per day This when added to the amounts in the stools and urine totals 2 2 milligrams per 24 hours This does not take into account growth in infants and children pregnancy or loss of iron through hemorrhage Furthermore it is based on the assumption that conservation of the metal is 100 per cent in other words that iron is used over and over again with complete re utilization It is probably correct that when normal conditions prevail there is little if any loss of iron from this cause

Intake of Iron—It is likely that the average normal diet contains 12 to 15 milligrams of iron per diem Only about 10 to 15 per cent of food iron is utilized as the absorbability is dependent on reducing substances in the diet and the gastrointestinal tract the degree of gastric acidity the state of the intestinal mucosa the condition of the iron reserves and possibly other unknown factors The amount of iron which is absorbed therefore amounts to between 1 2 milligrams and 2 25 milligrams which gives a narrow margin to create reserves and replace hemoglobin which may be lost by hemorrhage For example one teaspoonful of blood 4 cc contains 2 milligrams of iron The iron balance therefore in humans provides a narrow margin on the positive side This is especially true in women and readily indicates why iron deficiency anemia is observed so commonly in females

Absorption of Iron.—Iron is absorbed chiefly in the duodenum and jejunum and to a lesser extent in the stomach, ileum and possibly in exceedingly small amounts from the colon. It has been shown by Moore (38) that 6.5 per cent of iron is absorbed when given in the ferric form and 26 per cent when in the ferrous form. The importance of hydrochloric acid in the gastric secretions with reference to the absorption of iron is not entirely clear, although it is thought that this acid facilitates the absorption of the metal. This may be accomplished by preventing the formation of the insoluble iron compounds such as iron phosphate and the assistance it gives in dividing the iron into small particles.

Recently Moore and Dubach (39) have studied the absorption of radioactive iron Fe 59 in food and have concluded that about 10 per cent of the dietary iron is absorbed in normal males. There is *no increase*

TABLE IV

RADIOACTIVE IRON CONTENTS OF TISSUE AND BLOOD

Per Cent of Total Amount Fed (23 Hours After Last Feeding)

	Anemic Dog	*Normal Dog*
Liver	0.4	0.03
Spleen	0.0	0.02
Marrow	3.0	0.03
Plasma	0.3	0.01
R.B.C.	9.0	0.06
Total Absorbed	12.7	0.15

TABLE IV.—The information given above illustrates the action of the intestinal mucosa to absorb iron only when there is a need for the metal in the body. By means of radioactive iron it was determined that a normal dog would absorb only 0.15 per cent of a total dose of iron whereas in a dog made anemic by bleeding there was absorption of 12.7 per cent of the total amount of iron administered.
(Hahn, Bale, Lawrence and Whipple. Courtesy *Journal of the American Medical Association*.)

in the amount of such iron which is absorbed in patients with hypochromic anemia. If, however, ascorbic acid is given in doses of 1.0 gram *or if it is provided in the form of 200 cc. of grapefruit juice* or orange juice, about 70 per cent of the food iron is absorbed. These same investigators did not find that the administration of 60 cc. of 10th normal hydrochloric acid increased iron absorption.

As previously stated, if 10 to 15 per cent of the food iron is absorbed and the requirements of healthy males is 1.0 milligram and females 1.0 to 2.0 *milligrams, this should provide approximately the correct amount* of iron which is needed daily. The margin of safety is narrow, however, and any added loss of iron, such as repeated small hemorrhages, would throw the individuals, especially females, in which the balance is slight, into a depletion of iron reserves and an iron deficiency anemia.

The Transportation of Iron in the Circulating Blood—Iron which is absorbed from the intestinal tract is distributed throughout the body by the plasma of the circulating blood. The acid soluble iron in the plasma usually designated serum iron does not exist in the free state but is bound to a β 1 globulin (*10, 11, 12, 13, 41*). This protein of the plasma which has the capacity to combine and transport the serum iron has been designated by the following names: β 1 metal combining protein (*44*), siderophilin (*45*) and transferrin (*46*). The entire subject is discussed in detail by Laurell (*47*).

It is known that the plasma can combine with iron in vitro or in vivo in a certain amount which is called the saturation limit. One molecule of the *iron binding protein can combine with two atoms of iron*. The iron binding capacity of the serum has been determined to vary between 300 and 360 gamma per cent (*10, 12, 11, 18*) and hence the total amount of iron in the circulating plasma is between 2 and 3 milligrams. This is because the iron binding capacity of the plasma is usually *only* about 33 per cent utilized (*19*).

The function of the iron binding protein is to transport iron from the intestinal mucosa, the hemoglobin destroying organs of the body and the iron depots to the bone marrow where it is needed for hemoglobin synthesis. It has not been determined however whether the iron combining protein serves only as a carrier of iron as hemoglobin does for oxygen or if it delivers iron to different organs of the body as a result of entering into metabolic processes. As stated by Laurell (*47*) two different hypotheses have been advanced to explain the process by which the iron leaves the blood stream in the iron consuming organs: (1) that the whole complex of iron and its binding protein leaves the blood channels through the relatively permeable capillaries or (2) that the *iron binding protein serves as a real transporter of iron and only iron ions* leave the blood stream. In the opinion of Laurell (*47*) the data thus far collected support the hypothesis that iron leaves the blood stream in ionized form and that the iron binding globulin is simply a carrier of iron just as hemoglobin transports oxygen.

In iron deficiency anemia the amount of iron binding protein is somewhat decreased and the saturation of the protein may be as low as 10 per cent (*42, 49*). According to Cartwright and Wintrobe (*48*) the protein of the blood stream acts as a protective mechanism against the toxic effects which may arise from the injection of iron. *It is known that* the toxic effects which follow intravenous iron administration occur when the amount of injected iron exceeds that which can be combined with the iron combining protein of the plasma.

***Ferritin, Apoferritin,* and Hemosiderin and Their Relation to the Transportation and Storage of Iron**—Ferritin first discovered by Laufberger (*50*) is an important iron containing compound. It is readily

isolated from horse spleen. The material is a brown protein which may contain as much as 23 per cent dry weight of iron. When the iron is removed without damaging the colorless protein, the iron free substance is called apoferritin. It may be crystallized with cadmium sulfate and has a molecular weight of 460,000. Ferritin is thought to have two important functions with reference to iron metabolism. First, undoubtedly its primary purpose is related to the storage of iron in the body. The second is concerned with iron absorption. It has been established that the mucosal cells of the gastro intestinal tract control the amount of iron which is absorbed. According to Granick (35) the formation of ferritin in these mucosal cells is in some manner associated with the production of a mucosal block in the mucosa, thereby preventing the excessive absorption of iron. *Hemosiderin* is a protein material containing iron and related to ferritin. It is suggested by Granick (35) that the formation of hemosiderin may be pictured as an abnormal stage of iron deposition beyond that of ferritin. That is, if iron enters too rapidly into a tissue for apoferritin synthesis to keep pace with the entry of iron, or if the tissue is already saturated with iron, it becomes heaped up in granules as hemosiderin. The absorption of iron, according to the view of Granick (35), occurs in the ferrous form from the lumen of the gut into the mucosal cell. *This process is strictly one way.* It is probable that the iron thus absorbed is rapidly converted into ferritin by combining with the non iron containing apoferritin. The ferritin is then reduced to ferrous iron and enters the blood stream where it is oxidized to the ferric state and becomes attached siderophilin (blood protein) in the presence of carbon dioxide.

The views of Finch (51) and his associates on the storage and transportation of iron are as follows: reserve iron is considered to be tissue iron which is available for the synthesis of hemoglobin when the need is present. Such iron is located intracellularly in a protein complex as ferritin and hemosiderin. They believe that when the cell is functionally intact such iron is available for general body requirements. Iron is transported to and from the various body tissues by a globulin of the serum; surplus iron carried by this globulin is deposited largely in the liver. An increase in the reserve deposits of iron may be accomplished by two mechanisms. First, it is known that the body is unable to excrete significant amounts of iron. As a result of a decrease in the circulating blood iron in association with any anemia except those due to blood loss or iron deficiency, a shift of iron to the tissue compartments occurs amounting to 100 to 200 per cent increase in storage above normal. The total amount of iron in the body, however, remains the same; it is merely redistributed. On the other hand, if there is excessive absorption or parenteral injection of the metal, there may be an absolute increase in body iron which can be determined by examination of sternal marrow

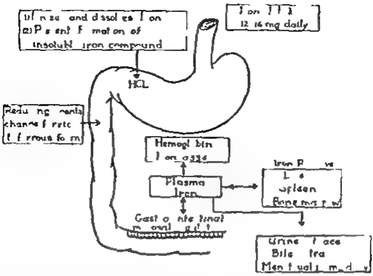

Fig 1 —The present day theory concerning the metabolism of iron in the body is given in the above chart Iron in its ferric form is taken into the body where in the stomach two important actions occur as a result of contact with the hydrochloric acid of the gastric juice (1) the iron compound is ionized and rendered more soluble (2) the hydrochloric acid prevents the formation of insoluble iron compounds such as phosphates *The iron then passes into the upper intestinal tract where it is apparently* reduced to the ferrous form and absorbed as such It is known that the amount of iron which is absorbed from the intestinal tract is regulated by the needs of the body *This control over absorption apparently resides in the gastro intestinal mucosa which* has the capacity to absorb or reject iron depending on the requirements at the time When iron is absorbed it is taken up by the blood plasma and 60 to 70 per cent of it *is combined to form the hemoglobin of the circulating blood* In addition a portion is stored and forms the iron reserves of the body in the spleen liver bone marrow and elsewhere Once iron has entered the body from the intestinal tract it normally does not leave except in the menstrual flow in the formation of the fetal tissues the milk and in exceedingly *small amounts in the bile and urine* It is estimated that normally the total iron content of the body is about 4 2 grams and that over 60 per cent is found in the circulating hemoglobin The iron reserves average about 0 3 gram (five grains) which is *a sufficient amount to provide for the regeneration* of between 600 and 800 cc of blood

or determination of the serum iron and saturation of the iron binding protein of the serum Iron absorbed from the gastro intestinal tract and that which is injected parenterally are stored predominantly in the liver According to Finch and his collaborators (*51*) colloidal iron is taken up by the reticuloendothelial tissues When the capacity of the liver to store iron is exceeded the serum iron then increases and the secondary tissue storage depots become saturated These observers express the opinion that large amounts of iron exert a toxic effect on tissues as evidenced by the development of fibrosis in the organs containing excessive amounts They believe that excessive iron absorption is responsible for the clinical and pathologic picture of hemochromatosis

Summary of the Metabolism of Iron —The average normal intake of dietary iron is between 12 and 15 milligrams daily of which about 10 per cent is absorbed largely from the small intestine Factors favoring

absorption are the ferrous state of the metal the presence of hydrochloric acid in the gastric secretions and other dietary factors as ascorbic acid which act as reducing agents Only small amounts of iron are lost from the body normally In adult males there is probably only about 1 milligram a day excreted in the stools urine and possibly some from the skin In the female the same amount is lost plus an average equalling about 1 milligram per day as menstrual blood It has been established probably as the result of the function of ferritin and iron protein complex present in the intestinal walls and elsewhere in the body that the metal is normally absorbed as needed After absorption it is carried by an iron binding globulin of the blood which normally is only about 33 per cent saturated to the bone marrow where it is synthesized into hemoglobin Iron is stored and available for hemoglobin synthesis in the tissues as ferritin and probably as hemosiderin which is a less labile form As the amounts absorbed and excreted are closely balanced it is apparent that any continued loss of even small amounts such as contained in 4 to [illegible] cc of blood daily will create a negative iron balance and produce an iron deficiency anemia This occurs when the iron reserves estimated to be between 600 and 1000 milligrams of iron represent sufficient quantities to participate in the formation of 1200 to 2000 cc of blood

Iron Metabolism in Relation to the Hypochromic Anemias—The fundamental and most important cause of iron deficiency anemia is the inability of the body to synthesize hemoglobin in normal amount rather than a diminished red blood cell production Our present knowledge indicates that the synthesis of hemoglobin is performed entirely in the erythrocyte which lies intravascularly in its developmental stage (*52*) This process according to Finch and his associates requires four to six days (*53*)

It is known that there are three main types of material which make up the hemoglobin molecule These are protoporphyrin globin and iron *Protoporphyrin* is produced without difficulty and there are no studies to suggest that a lack of this material in man is ever the important cause of an anemia (*54*) Globin is also produced with ease in the body and there is evidence to show that when there is general protein depletion blood regeneration will occur and the protein quota supplied for this purpose despite a general shortage in the body (*55*) On the other hand there is *frequently a lack of sufficient iron in the* body for the purposes of hemoglobin synthesis and consequently iron deficiency anemia is one of the most commonly encountered types throughout the world

With such a narrow margin of safety in the intake to provide for all of the iron requirements of the body and in addition create reserves it is not surprising that any situation which calls for more iron such as continued loss of even small amounts of blood growth or pregnancy may result in a negative iron balance and an iron deficiency anemia

Hemorrhage as a Cause of Iron Deficiency Anemia.—Chronic hemorrhage is the most common cause of this variety of anemia in both sexes in adult life. A loss of blood means the loss of iron, as almost 60 to 70 per cent of the total amount of iron in the body is in the serum and hemoglobin of circulating blood. Moreover, the element is found in the blood in a concentration of at least five times that known to exist in any other tissue.

Acute hemorrhage in a healthy adult does not ordinarily cause an iron deficiency anemia, because nature has wisely provided an ample iron reserve in the body. This makes available an adequate amount of the metal to permit regeneration of blood from an acute loss without augmenting the intake. For example, if a healthy adult lost as much as one third of the total amount of blood in the body, the hemoglobin would return to normal just as rapidly without the addition of iron to the intake as with it, provided the bleeding was controlled. This is because ordinarily the necessary amount of additional iron is stored for such purposes in the body of the normal adult. It is estimated that a healthy person could lose up to 33 per cent of his total blood volume and regain a normal hemoglobin by utilizing the normal iron reserves alone for this purpose.

It is chronic, long continued bleeding for months, in the form of small unnoticed quantities of blood, which is likely to lead to an iron deficiency anemia. Almost 50 years ago the astute observer, James B. Herrick of Chicago (56) recognized the great importance of repeated small hemorrhages as a cause of severe anemia and reported his observations in the *Journal of the American Medical Association*. He observed four cases of severe anemia associated with bleeding hemorrhoids and emphasized that a severe anemia producing pallor and marked weakness may be due to recurring small losses of blood from a condition as easily recognized and easily remedied as hemorrhoids.

In the female, iron deficiency is most often due to uterine hemorrhage which may be recognized as excessive by the patient, but in many instances she is not aware that there has been an abnormal loss of blood from this source. This is because the average woman has no means of estimating how much blood is normally lost at any given menstrual period. Furthermore, as the periods may occur at the regular intervals and the blood loss be only slightly greater than normal, it is not surprising that such mild excessive bleeding should escape notice by the average woman. If it is long continued, it may well be the explanation of an iron deficiency anemia which sometimes appears to be of obscure origin. In all female patients with anemia, therefore, during the period of reproductive life, a definite statement should be included in the history relating to the exact interval between periods, the duration of the menstrual period, and the number of pads which are used daily. In this

way only is this important information made available with any degree of accuracy. It has required an amazingly long time for physicians to realize that the abnormally large loss of blood at menstrual periods which are commonly regarded as normal by the patient may be an important cause of a profound iron deficiency anemia (see p 72). In many instances there is no recognizable cause to be found for the menstrual abnormality, although the possibility of hypothyroidism should always be kept in mind. In others the bleeding may be due to a uterine fibroma and less frequently cancer or some other organic condition.

In the male the most common source of blood loss is from the gastrointestinal tract. This may be due to bleeding esophageal varices, peptic ulcer, gastric cancer, malignancy in the colon, chronic ulcerative colitis or bleeding hemorrhoids. In certain obscure instances it may be associated with ulcerations in a diaphragmatic hernia, to varicose veins in the intestinal tract, to intestinal telangiectases, or a gastric polyp, or polyps in the colon which are not always detected by gastro intestinal x rays.

It should be axiomatic that if an adult has an anemia with a color index of 0.6 or less the possibility that it is due to chronic bleeding is great. In the female it may be associated with excessive loss of blood from which she considers to be normal menstrual periods, and in the male it is likely to be from the gastro intestinal tract. This may readily be established by testing for occult blood in the stools, subjecting the patient to gastro intestinal x ray studies and sigmoidoscopy, and keeping *in mind the fact that certain lesions in the stomach, intestines and colon* may escape notice in the roentgen ray examination.

Deficiency of Dietary Iron.—It is not likely that a deficiency of dietary iron alone will cause a depletion of the metal in the body to such an extent that a hypochromic anemia will result. It may be, however, an important contributing factor particularly in women and children. From a theoretical standpoint it is doubtful if a healthy male adult could possibly partake of a diet which would be so low in iron as to cause hypochromic anemia. It is extremely unlikely also in the female although other additional factors, such as pregnancy and lactation, and the loss of iron in menstrual blood, make a dietary deficiency of iron of greater importance in this sex. In the male adult the only loss of iron normally is the small quantity in the stools, the minute amounts in the urine, and possibly traces in the sweat. This is estimated to total only about 1 milligram daily. It is inconceivable that any person could partake of a diet containing as little iron as this either by accident or design.

Two matters of importance concerning the relation of the diet to the iron deficiency anemias should be emphasized, namely (1) the clinical observation is substantiated that a diet low in iron is rarely by itself a cause of an iron deficiency anemia and (2) that the dietary intake

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pregnancies occur there is a definite increase in the demands of the body for iron This is now recognized by all hematologists as true and these factors therefore are regarded as highly significant ones in the production of the hypochromic anemias An excellent comprehensive review with a bibliography of 368 articles of the relationship between iron metabolism and the hypochromic anemia of infancy has been published by Josephs (57A)

The increase in the iron requirements during the periods of growth are attributed to two conditions namely (1) to the augmented total cellular content of the body and (2) to the increase in the total blood volume As iron is known to be present in every cell in the body it is logical to assume that with growth there must be some increase in body iron due to the added number of total cells present It is not thought however that the total amount of iron in the body is greatly increased as a result of this A much more important need for iron is created by the greater blood volume which develops with the growth in body size Heath and Patek (58) have estimated that the total blood volume has an average increase of 340 cc between the fourteenth and fifteenth years This when combined with an estimated menstrual loss of 650 cc in females during an interval of a year would total 1000 cc or one fourth of the total blood volume at that age which must be produced by the body in addition to the other normal demands While the iron necessary for the synthesis of this additional hemoglobin is ordinarily supplied by the average normal diet a hypochromic anemia will appear at this time if the dietary intake is insufficient or if any additional factors such as an achlorhydria a chronic infection or hemorrhage are present

One of the most frequently encountered types of iron deficiency anemia is observed in infants This results chiefly from the combination of rapid growth and a diet consisting exclusively of milk which is known to be poor in iron Other factors may also contribute to this variety of anemia and these will be discussed under the section dealing with the Iron Deficiency Anemia of Infants

The Role of Pregnancy in Producing Iron Deficiency Anemia —This *is a common form of iron deficiency anemia which is discussed more* completely under the section on Anemias of Pregnancy" It is known that an additional amount of iron is necessary during pregnancy in order to form the fetal tissues including the blood It should be remembered however that there is some conservation of iron during gestation due to the absence of the menstrual periods Although there is not entire agreement in regard to this it seems fair to state that the increased demands associated with a normal pregnancy including the average blood loss at the time of delivery exceeds by two or three times the iron loss due to normal menstruation over an interval of nine months Hence during pregnancy if there is in addition a deficiency of iron in

however may be reduced to such a low level that there is only a very small margin of safety If some other etiological factor then comes into play such as an infection or loss of blood or perhaps only the presence of an achlorhydria which impairs the absorption of the metal in the diet then a significant depletion of iron occurs in the body and a hypochromic anemia will develop

The importance of a subnormal intake is emphasized by the knowledge that the incidence of these anemias is proportional to the degree of malnutrition among the inhabitants of any region It is possible therefore to predict with reasonable accuracy that in the countries in war areas which are subjected to an inadequate food intake representing famine conditions in some instances there will be a striking increase in the iron deficiency anemias especially in women and children Recent information secured by Mackay and her associates (27) who studied the hemoglobin values of over 1000 women and children living in London and English rural areas during the war period are of interest in this connection It was found that in children from six months to eighteen years of age and in women housewives hospital nurses medical students and factory workers there was a decrease in hemoglobin values as compared to those prior to the war and this decrease was attributed to wartime diets which were presumably deficient in protein and iron Indirect evidence that the diets are not entirely adequate is also available from Germany for in that country during the war it was often necessary to administer iron (57) to patients with pernicious anemia who were receiving liver treatment This has never been necessary in the United States where an adequate diet is available and suggests that there was in 1943 a deficiency in the German diet of iron containing foods

Davidson and others (26) reported the results of a similar study on the hemoglobin level of 831 infants preschool and school children of the working class families living in Edinburgh Scotland The findings were compared with a similar study carried out before the war It was found that after three years of wartime restrictions no change in hemoglobin values had occurred in infants but that a decline was present in older children They conclude that during peacetime the chief factor influencing nutrition is the economic status of the family but that under war conditions the food rationing and the difficulties of obtaining unrationed foods are the most important factors irrespective of income

Increased Demand for Iron Due to Growth, Pregnancy, and Lactation.—It is generally agreed that the iron deficiency anemias are much more prevalent in infants children and adolescents during the period of growth and women when in the reproductive period of life This at once suggests that at the stages of greatest growth which are during infancy puberty and the period when menstruation is present and

Fig 2 —A diagrammatic representation of the important theoretical aspects of iron metabolism in a female from birth until after the menopause emphasizing the important causes of iron deficiency at different age periods It shows the iron requirement to be relatively high in infancy followed by a period of diminished need until the beginning of rapid growth at about the age of 10 years This increased demand which is due to rapid growth and menstruation usually continues at its highest level between the ages of 14 and 19 years After maximum growth is attained the need for iron remains stabilized and the demand fluctuates depending on various factors such as excessive loss of blood pregnancy lactation and infection The reserves are represented by the lowest line They vary depending on the balance between the iron intake and the need for the metal With serious encroachment up on the iron reserves a sufficient amount is not available for the formation of hemoglobin and hence an iron deficiency anemia develops It will be noted that the iron requirement falls rapidly after the menopause due to the cessation of menses Iron deficiency anemias may occur of course after this period of life but they are then usually associated with chronic hemorrhage due to organic disease such as uterine malignancy peptic ulcer cancer of the stomach hemorrhoids etc The chart emphasizes the reasons why iron deficiency anemia is most common in the female at the periods of growth menstruation and child bearing

By means of radioactive iron it has been demonstrated that in the presence of an infection the utilization of iron for hemoglobin synthesis is impaired and that this condition prevails despite the injection of large amounts of iron intravenously . Instead of being utilized for the synthesis of hemoglobin the metal is diverted to the spleen and liver It is their opinion that hypoferremia is one of the most constantly occurring findings in patients with infection In a recent study it has been found by Cartwright *et al* (68) that in addition to the bacterial and sterile abscesses other agents such as histamine epinephrine fracture anaphylactic shock and mild stress may also cause acute hypoferremia in dogs . Furthermore the injection of adrenocortical extract and adrenocorticotrophic hormone also produce a hypoferremia From these observations and other experiments which they performed on dogs it is assumed that one of the factors concerned in the regulation of the plasma iron level is the *adrenal cortex* It is their belief that under conditions of chronic stress the hypo

the diet a hypochromic anemia of considerable extent usually develops This is particularly true if the pregnancies are repeated at frequent intervals and if lactation is long continued

Impaired Absorption of Iron.—It is known that impaired absorption of iron may contribute to the severity of an iron deficiency and this is regarded as due to at least two different mechanisms In chronic diarrhea there may be a loss of iron through the bowels on account of the rapidity with which the contents pass through the intestine Just how important this is has not been accurately determined, although theoretically it should be of some significance It is known, moreover that anachlorhydria is definitely related to the absorption of iron as is ascorbic acid (35) and possibly other unidentified dietary substances Apparently the efficiency of the absorption of iron from the gastro intestinal tract has some relation to the hydrochloric acid content of the gastric juice for if it is absent or reduced absorption of the metal is less efficient Although the organic acids provided by fermentation will replace to some extent the hydrochloric acid in rendering food iron more absorbable their action is much less efficient It is apparent that anachlorhydria therefore will have the effect of altering a high iron diet to one low in iron Although impaired absorption of iron will probably not in itself cause a hypochromic anemia it may be an important contributing secondary factor

The Relation of Infection to Iron Deficiency Anemia.—Undoubtedly there are other important contributing factors to the production of these anemias in addition to those that have been discussed Clinical observation has indicated clearly that one of these is the presence of acute or chronic infection Certainly it will intensify an anemia which is already present and furthermore it can be the sole cause of an anemia In addition if an anemia is treated with a specific remedy as iron or anti pernicious anemia medication the anticipated response may be less when an infection is present (A further discussion of the relation of infection to anemia is to be found under the heading of The Etiology of Simple Chronic Anemia" (page 161))

The relation of infection to an iron deficiency in the body and a resultant anemia has been investigated by Wintrobe and his associates in a series of publications which have appeared in recent years (59 60 61 62 63 64 65 66 67 68) They find in dogs that an acute transient reduction in the blood iron occurs following the experimental production of an infected (staphylococcus) or sterile (terpentine) intramuscular abscess This indicates that the hypoferremia is not necessarily due to bacteria or their products These same investigators believe that they have produced evidence which indicates that in infection the reticulo endothelial system is stimulated to store iron which prevents it from being readily available for the synthesis of hemoglobin

many instances the patients complain only of ease of fatigue and are much surprised to learn that an anemia is present. One patient entered the hospital on account of an acute respiratory infection and the routine examination of the blood disclosed a hemoglobin of 50 per cent. She had been working as a graduate nurse on eight hour duty without difficulty. On close questioning she admitted having fatigue but she had never felt any other way in her life and thought that was a normal state of health. In most patients however there are definite complaints although usually they are not of such an extent as to prevent them from doing some housework or at least in a half hearted manner to attempt to carry on a normal existence. Usually the chief symptoms are ease of fatigue and weakness pallor dyspnea on exertion palpitation mild vertigo an impaired appetite and vague digestive disturbances.

Physical examination usually reveals pallor in a person who may be undernourished or one who gives no evidence of recent loss of weight. Emaciation in these patients is not a prominent sign and in some cases especially of the so called idiopathic hypochromic anemia of middle aged women there may be moderate obesity. There is almost always a hemic murmur at the apex or base of the heart or both areas and other findings such as koilonychia which are considered under the descriptions of the various types of iron deficiency anemia.

BLOOD EXAMINATION

The characteristic findings in the blood in patients with iron deficiency anemia are those of a microcytic hypochromic anemia. There is often a striking decrease in the hemoglobin of the cells as compared to the reduction in the total red blood cell count. For example a characteristic finding would be 3.5 million red blood cells per cubic millimeter and a hemoglobin of 35 per cent which would give a color index of 0.5. The mean corpuscular hemoglobin concentration is usually between 20 and 30 per cent and may be even lower. A low color index and mean corpuscular hemoglobin concentration is always highly suggestive of an iron deficiency anemia. It can occur however in another condition namely Cooley's anemia which is not related to a disturbance of the metabolism of iron.

There is almost always a decrease in the size of the cells below normal as indicated by a mean diameter which characteristically measures between 6.2 and 6.7 microns a mean corpuscular volume between 60 and 80 cubic microns and a Price Jones curve with a pronounced shift of the peak to the left. Other findings commonly observed are a saturation index of 0.75 to 0.90 and a mean corpuscular hemoglobin between the limits of 15 to 21 micrograms.

Examination of the stained blood film reveals the presence of small red blood cells which contain a reduced amount of hemoglobin. Unless the

ferremia is due to the removal of iron from the plasma by cells of the reticulo endothelial system These investigators warn that their conclusions are based solely on experimental evidence obtained in dogs It is possible that the same mechanism is operative in man but they emphasize that no direct evidence has been presented in their publications to prove this assumption

Pathology of Iron Deficiency Anemias—There is little that can be said regarding the pathology of the iron deficiency anemias because the condition is rarely fatal and few necropsies have been done on these patients prior to treatment Judging from the findings in animals that have been rendered anemic by repeated bleeding one would expect to find a deficiency of stainable iron in the liver spleen skin and bone marrow *provided iron therapy had not been given*

Suzman (69) reports the necropsy of a patient with the Plummer Vinson syndrome who succumbed following esophagoscopy with rupture of the esophagus and subsequent infection The hemoglobin had been 30 per cent and the red blood count 3 5 million per cubic millimeter just prior to death No gross pathological abnormalities were noted in the heart gastro intestinal tract *spleen pancreas suprarenals kidneys or* thyroid gland Mention was not made of the findings in the stomach The esophagus showed a definite fold of mucous membrane forming a mucosal band and it was thought that this accounted for the obstruction at the upper end of the esophagus and the complaint of dysphagia during life The mucosa and muscle of the tongue and esophagus showed definite histologic abnormalities consisting chiefly of hyperkeratinization of the epithelium with areas of desquamation and of degenerative atrophic changes in the underlying muscle The possibility is mentioned that the hyperkeratinization of the epithelium may have been due to a deficiency of vitamin A

A case (*70*) has been reported in a 50 year old woman who had been given iron for a period of three weeks and then died following an operation on the uterus for a myoma In this patient there was widespread atrophy of the mucous membranes of the tongue esophagus and stomach and hemorrhages in the mucosa of the latter viscus Gastroscopy during life has been reported by other observers (*71*) as showing a pale gray atrophic mucosa

The sternal bone marrow which has been described in more detail under the appropriate *section shows normoblastic hyperplasia*

The General Clinical Manifestations in Patients with Iron Deficiency Anemia Regardless of Its Causes—Symptoms and Signs—The complaints of patients with an iron deficiency anemia resemble those of any type of anemia and are directly proportional in intensity to the reduction in the hemoglobin Symptoms may be mild or almost absent despite the presence of a hemoglobin level which is well below normal In

mentary, Chlorotic Anemia of Infancy) —This is an exceedingly common type of iron deficiency and is due to the fact that there is a tendency for every infant to be in negative iron balance during the first six months of life The cause of this is an increased demand for iron at this time which is associated with rapid growth Also during this interval the iron intake may be low as a result of diet of milk only which is poor in this metal The requirements for increased blood formation must be met in such cases by the reserves of iron which have been stored during the last trimester of pregnancy and by the high rate of conservation of iron from the hemoglobin destruction during the initial two weeks of life

In general it may be said that such an anemia in infants is most prevalent at about the age of one year and that it results from the presence of one or more of the following factors

1 A maternal iron deficiency which results in the infant being born with a normal hemoglobin of the circulating blood but devoid of the normal iron reserves

2 Prematurity low birth weight or multiple births which are responsible for a deficient prenatal storage of iron in the infant and a greater demand for the metal during the first year of life because of rapid growth It is estimated that normally the blood volume is tripled and the hemoglobin doubled in the first twelve months following birth

3 A low iron intake due to prolonged artificial feeding exclusively with cow's milk which has a suboptimal amount of iron

4 Other etiological factors of importance may be infection anorexia achlorhydria and chronic diarrhea which interferes with absorption and utilization of iron

The iron deficiency anemia of infants ordinarily *does not occur before the fourth month of life* and should not be confused with the physiological fall of hemoglobin which begins shortly after birth and continues until the second or third month Such a condition is thought to be associated with a decreased need for hemoglobin in the circulation in the presence of the greater oxygen supply of extrauterine life This physiological fall of hemoglobin is roughly proportional to the weight of the infant and hence in premature infants at the third month it may be so great as to be regarded as pathological by some That this anemia is not due to an iron deficiency is shown by the fact that it will not respond to iron medication True iron deficiency anemia of infants corrected promptly by iron medication may be prevented often by administering iron to the mothers during pregnancy

CHLOROSIS

Definition —An iron deficiency anemia occurring in adolescent girls

General Statement Concerning the Disorder —This condition has had a curious history There can be no doubt that chlorosis did exist fairly

anemia is severe, the cells are of fairly normal shape and variation in size is not great. In untreated cases the reticulocytes are usually 1 to 2 per cent and there is rarely evidence of regeneration of the red blood cells as indicated by nucleated erythrocytes and diffuse or punctuate basophilia. Following the administration of iron there is characteristically an increase in the percentage of reticulocytes on about the fourth or fifth day of therapy. This is much less than is seen in the case of patients with pernicious anemia as the peak rarely exceeds 10 to 12 per cent.

There is no characteristic change in the leukocytes as the white blood cell count is usually within normal limits, but in chronic cases it may be reduced below 4000 per cubic millimeter. If there is a fresh hemorrhage of any extent it is not uncommon to have a slight leukocytosis with an increase in the neutrophils. The blood platelets are ordinarily normal in number but also in case of an acute hemorrhage they are likely to be increased for short intervals.

Bone Marrow.—The bone marrow is characteristically hyperplastic with a predominance of normoblasts. In contrast to the changes in the marrow in pernicious anemia, megaloblasts are lacking although young normoblasts may be noted. There is no important variation from normal in granulopoiesis. The normoblastic proliferation disappears following medication with iron.

Gastric Analysis.—Hypochlorhydria or achlorhydria is frequently present in patients with iron deficiency anemia. This statement requires some modification however as the state of the gastric secretions depends to a certain extent on the cause of the iron deficiency. For example, an achlorhydria is never found in association with peptic ulcer and yet an anemia of this type is not uncommon in this condition. Achlorhydria following the injection of histamine is almost always present in the so called idiopathic hypochromic anemia of women and it is usually permanent. It may also be observed occasionally in the hypochromic anemia of childhood. In chlorosis the acidity of the gastric juice is said to be normal or decreased.

In the severe cases of iron deficiency there is also a reduction or absence of pepsin but as one would expect the intrinsic factor of Castle has been demonstrated to be present (58).

Other Laboratory Findings.—The serum bilirubin is normal or may be slightly diminished as is the icterus index. The plasma proteins may be reduced and if the anemia is severe this accounts for the edema in some of the patients although if questionable pitting edema is disregarded this physical finding has not been common in my experience. The blood iron is usually reduced in proportion to the amount of hemoglobin.

VARIOUS TYPES OF IRON DEFICIENCY ANEMIA

Hypochromic Anemia of Infancy and Childhood (Nutritional Al

of a hypochromic anemia in an adolescent youth or adult male should always arouse the strong suspicion that chronic bleeding is present

Changes in the Blood —The typical changes are those of a microcytic hypochromic anemia Thayer (72) reported 63 cases with a red blood cell count averaging 4 0 million per cubic millimeter and an average hemoglobin of 42 per cent Cabot s (73) cases most frequently had a red blood cell count between 3 0 and 4 0 millions per cubic millimeter and a hemoglobin between 21 and 42 per cent

Certainly it is very rare for us to see at present such a severe degree of hypochromic anemia in adolescents although mild examples of this type are not uncommon In my experience the red blood cell count is more often in the vicinity of 3 5 to 4 0 millions per cubic millimeter and the hemoglobin between 50 and 60 per cent It has been found by Heath and Patek (58) in the routine examination of 38 presumably healthy student nurses between the ages of 18 and 23 years that 26 per cent had a moderate anemia with a hemoglobin between 70 and 79 per cent They also state that a hypochromic anemia of severe grade and responding to iron has been fairly frequently discovered in adolescent girls who entered the hospital for treatment of some other disease such as pulmonary tuberculosis pleurisy with effusion lobar pneumonia and pyelitis This corresponds very closely with our experience at the University Hospital in Ann Arbor both with respect to the student nurses and adolescent girls admitted to the hospital for one reason or another

Treatment —Iron is specific for the condition It should be administered over a period of months and the patient observed for recurrences In a few patients in my experience there has been a hypermenorrhea which has apparently prevented the proper response to this medicament In such patients one should suspect the possibility of hypothyroidism and if the basal metabolic rate is significantly lowered a cautious trial of desiccated thyroid gland is worthwhile as it may control the excessive bleeding

Hypochromic Anemia of Chronic Blood Loss

This condition has been previously described in detail under the heading of Etiology of the Iron Deficiency Anemias and further detailed discussion is unnecessary except for a few statements concerning this condition which should be repeated for the purpose of emphasis In the first place this is the most prevalent type of anemia in the United States and probably throughout the world It should be kept in mind constantly therefore that when a hypochromic microcytic anemia is detected probably chronic hemorrhage is at fault In women this is usually uterine and in males it is most frequently from the gastrointestinal tract As previously mentioned among the more common causes for the latter are peptic ulcer cancer of the stomach esophagus or

commonly in the past as evidenced by careful hematological observations In the section on blood diseases in the 1915 edition of Osler and McRae System of Medicine Richard Cabot defines chlorosis as a disease of unknown cause, occurring only in young girls usually between the ages of 15 and 25 years and producing a moderately severe anemia In summing up the symptomatology he states that the patients complained especially of dyspepsia, with more or less perversion of appetite, of constipation muscular weakness and shortness of breath (often with palpitation and edema of the extremities) of headache vertigo tinnitus insomnia and various pains possibly of neuralgic nature According to Cabot the menses were supressed irregular or over profuse He states further that It takes the eye of faith to see any justification for the title of the disease from the Greek word meaning green It was his opinion that if one exercises a great deal of imagination one might possibly see the slightest imaginable tint of olive green in the shadow beneath the chin but that is all

In 1915 when this article was written Cabot states that the most remarkable thing about chlorosis was that it was disappearing at least in the United States There is a tendency even now to regard it as a rather vague and mysterious syndrome which existed only in the past This is not however entirely true If one does not pay too much attention to the significance of the name as indicating an important symptom it may be said that at least mild chlorosis as defined in the first sentence of this section is not a rare disease in this country at present I can honestly state however that never in such a patient have I seen the slightest suggestion of a greenish color or noted a history of a perverted appetite upon which the older writers seemed to place so much weight from the standpoint of diagnosis

In girls of the adolescent age, it is easy to understand why an iron deficiency should develop This is because there is an increased demand for iron associated with the rapid growth at that age and in addition with the onset of menstruation there is the added factor of blood loss which may be excessive If the patient should have a poor appetite or exist on a diet which was low in iron or develop an infection or have an achlorhydria there would be added causes for the iron deficiency

Hypochromic anemia in adolescent and adult males is a very rare condition unless chronic bleeding is present This usually occurs from the gastro intestinal tract although repeated epistaxis may account for it It is possible that in males the combination of two or more factors such as rapid growth a diet inadequate in iron achlorhydria and chronic infection may produce a hypochromic anemia I saw such an anemia which responded to iron in a youth of 16 who had grown rapidly and had a persistent sinus infection The diet did not appear to be abnormal but a gastric analysis was not done In general however the presence

theoretically there is no reason why it should not appear in males That it should be rare in this sex is understandable however because the iron requirements in adult males are so much less than in females

According to Wintrobe and Beebe (74) 60 per cent of the affected individuals are between 30 and 50 years of age while 82 per cent are 20 to 50 years It is generally agreed that definite constitutional and hereditary trends are present in individuals with this disease which are similar to those of pernicious anemia Often there is a family history of anemia and some families have been observed in which there have been cases of hypochromic anemia with achlorhydria which later have changed to pernicious anemia and other members of the family in whom evidence of true pernicious anemia has been present from the onset (74)

It is now generally agreed that the term "idiopathic hypochromic anemia should be abandoned As Moore says (75) there is nothing mysterious about the development of an iron deficiency in adults The chief causes of excessive loss of iron from the body and the development of this type of anemia are repeated pregnancies chronic hemorrhage or even normal menstrual blood flow The same observer states that other factors may contribute to the iron deficiency For example an inadequate diet or defective absorption from the intestinal tract may enhance the deficiency Furthermore an achlorhydria may also be of importance as there is then less ionization of the food iron and more prompt precipitation of the metal in the small intestine None of these etiological factors alone however cause hypochromic anemia They must be combined with loss of iron from the body usually due to chronic hemorrhage and less frequently to repeated pregnancies in order to create an iron deficiency and a resultant hypochromic anemia

In summary there are now considered to be at least four chief etiological factors all of which play a role in any given patient They are as follows

1 Bleeding usually unnoticed most commonly menorrhagia but also from other sources such as hemorrhoids and epistaxis

2 A dietary deficiency of iron

3 Malabsorption of iron due to the almost invariably present achlorhydria or hypochlorhydria

4 Frequent pregnancies at relatively short intervals

Symptoms and Signs —The onset is always insidious and the patient is rarely able to state the exact time when the initial complaints were first noticed Usually they have been present for years and often the statement is made that they have never been well and strong In some instances this is probably literally true for it is known that an iron deficiency anemia may exist almost from birth Hence the patient may have had in succession with varying degrees of intensity the hypochromic anemia of infancy the chlorotic syndrome of adoles

colon hemorrhoids esophageal varices in association with cirrhosis of the liver and chronic ulcerative colitis Epistaxis may also be an important cause Occasionally some unusual condition may account for the loss of blood from the gastro intestinal tract Among these may be mentioned diaphragmatic hernia polyps in the stomach or intestines or varicose veins in the intestines

An additional cause which may occur at all ages and in both sexes in certain areas of the world is hookworm infestation For many years this anemia was considered to be of some mysterious origin, such as a toxic effect of the parasite on the blood forming organs but now it is known to be due largely to chronic loss of blood In some instances low dietary iron and achlorhydria may play secondary roles It responds promptly to iron even before the worms have been removed

In women the most frequent cause of hypochromic anemia is hypermenorrhea although they may give no history even on close questioning that this is the source of the abnormal blood loss It is known however that while the average loss of menstrual blood per month varies between 30 and 60 cc it may be increased five times this amount without it being appreciated that it is abnormal

Even though an iron deficiency anemia may be due primarily to chronic blood loss in any given patient it should be kept in mind that other important factors may also be of importance These are an achlorhydria which interferes with the normal rate of absorption of iron an inadequate iron intake in the diet repeated or chronic infections and pregnancy and lactation

In almost all instances there is a gratifying response of such an anemia to the proper iron therapy Occasionally however the loss of blood may be so great that even though the proper amount dose of iron is given it may fail to compensate for the large amount lost by excessive hemorrhage

Chronic Hypochromic Anemia

Synonyms—Idiopathic hypochromic anemia simple achylic anemia primary hypochromic anemia chronic microcytic anemia essential hypochromic anemia

Definition—A chronic microcytic hypochromic anemia almost always occurring in women between the ages of 20 and 50 years who have an achlorhydria or a reduction in the amount of free hydrochloric acid in the gastric juice The condition is due to a deficiency of available iron in the body resulting from diverse causes It responds uniformly and favorably to iron therapy

Etiology—The syndrome occurs almost entirely in females in fact some authorities insist that it is never present in males As it is now thought that it is due to an iron deficiency often associated with an achlorhydria chronic hemorrhage and repeated pregnancies, it must be admitted that

exaggerated longitudinal striations and increased thinness and brittleness of the nails He states that these findings are also present in cases of hypochromic anemia lacking typical koilonychia With the exception of flatness of the nail such changes have not been conspicuous enough in my experience to suggest the diagnosis of hypochromic anemia I have observed however flat nails which should be considered as a less marked phase of koilonychia Such a change has been designated platonychia When this condition is observed it should suggest the presence of an iron deficiency anemia but it is not as strong evidence of this condition as koilonychia

According to Clarke (76) this striking change in the finger nails was first described by Ball (77) in 1874 who presented a case to the Society of Biology in Paris but did not assign a name to it The name spoon nails" was suggested in 1896 by Crocker (78) and the designation of koilonychia was introduced in 1900 by Heller (79)

Koilonychia is commonly observed in persons with an iron deficiency which is most frequently dependent on chronic blood loss As Clarke states (76) women until the menopause require four times as much iron as men do and hence hypochromic anemia and also koilonychia are more common in the female sex Certainly the presence of koilonychia should at once excite the suspicion that a person has an anemia of the iron deficiency type although this is not always the case There is evidence to indicate that an iron deficiency can exist in a person in whom the blood is normal or even in the presence of polycythemia For example the studies of Waldenstrom and Hallen (80) have shown that the condition in the nails is not due to the anemia but both the hypochromic anemia and the koilonychia are the result of an iron deficiency in the body as indicated by a low serum iron They claim to have detected evidences of iron deficiency in persons without an anemia as indicated by a low serum iron Three of their cases had koilonychia without anemia and a deficiency of iron in the blood serum and furthermore the nail disturbances disappeared with iron therapy They conclude that sideropenia can affect either the epithelial tissues or the hematopoietic system On this basis the koilonychia occurring in a patient who had polycythemia rubra vera is explained by Glazebrook (81) This observer argued that during the period in which there was great activity on the part of the bone marrow there was a demand for iron in the hyperplastic hematopoietic tissues which was excessive and consequently the serum iron was low He noted that treatment of the polycythemia with the roentgen rays reduced the red blood cell count and greatly increased the serum iron With this there was a disappearance of the koilonychia

In my experience the spoon nails tend to disappear in persons with hypochromic anemia when iron is administered and thus is the conclusion of other observers A male age 46 whose case is reported by Clarke (76)

cence the hypochromic anemia of pregnancy and chronic hypochromic anemia It is interesting to note that usually such a patient s troubles are over from this standpoint at the termination of the reproductive life In some instances apparently there has been an adjustment to the low hemoglobin values in the blood and consequently it may be surprising to find that the clinical manifestations are vague and relatively scanty in the presence of even a moderately severe anemia

The symptoms are usually those associated with any anemia of which asthenia and ease of fatigue predominate Other complaints are mild chronic indigestion characterized by vague upper abdominal distress and often the passage of soft mushy stools low resistance to respiratory infections emotional instability and vague aches and pains Menorrhagia is common as on careful questioning it will be found that about three fourths or more of these women have an excessive loss of menstrual blood It should be emphasized that this is an important aspect of the history which is often overlooked unless particular attention is given to it A certain amount of glossitis and atrophy of the papillae of the tongue occurs in about one third of the patients but rarely do such changes attain the prominence observed in pernicious anemia Numbness and tingling of the four extremities may also be present but it differs from that of pernicious anemia as only 15 to 20 per cent have such complaints and it is in a milder degree and less persistent

Physical examination shows a variable degree of pallor without evidence of a yellowish tint usually fair nutrition or moderate emaciation and frequently oral sepsis which does not in my opinion bear an etiological relationship to the disease In some patients there is an acute glossitis which manifests itself as an abnormal redness either confined to the tip of the tongue or involving the entire organ While other patients may have no symptoms referable to the tongue there may be atrophy of the papillae over the dorsum which gives the characteristic smoothed out appearance

Koilonychia —A curious concavity of the finger nails designated koilonychia is observed in from 15 to 30 per cent of all patients with idiopathic hypochromic anemia The term koilonychia which is derived from the Greek meaning spoon nails denotes a condition characterized by a central spoonlike concavity of the finger nails with flat lateral margins and a tendency to eversion of the end of the nail Any number of fingers may be affected and in varying degree It is said to involve the toe nails in rare instances It is my impression that the thumb and fore finger are most likely to show the more pronounced changes I have never seen such an abnormality of the toe nails although so often toe nails are misshapen and hence it is difficult to state positively if mild degrees of koilonychia are present According to Clarke (76) associated changes which are commonly observed in the finger nails are flattening

country is designated with the Plummer Vinson Syndrome In 1922 Porter P Vinson of the Mayo Clinic reported (65) 69 cases of this condition under the title of "Hysterical Dysphagia" According to Suzman (69) the disorder has been previously described by Kelly and Patterson in 1919 in England in two separate papers entitled "Spasm at the Entrance of the Oesophagus (89) and A Clinical Type of Dysphagia" (90) Except for the dysphagia all of the clinical manifestations of this condition are entirely similar to those of idiopathic hypochromic anemia

The etiology of the dysphagia is in dispute The current theories regarding its cause are 1 that it is a hysterical manifestation 2 that it is spasm or failure of the pharyngo-esophageal sphincter to relax resulting from inflammatory involvement of the nerve supply in the pharyngo esophageal region or involvement of Auerbach s plexus 3 that webs bands or raised folds of mucous membrane are the definite cause of the obstruction 4 that it is associated with a condition of hyperkeratinization of the epithelium of the tongue hypopharynx and esophagus with areas of desquamation and atrophic degeneration of the underlying muscles The arguments for and against these views and a summary of the literature are given by Suzman (69)

The relationship of the anemia to the dysphagia is not entirely settled at present It is generally claimed that the anemia is on the basis of the dysphagia which prevents the ingestion of a normal diet containing an adequate amount of iron Undoubtedly it is true in all cases that the anemia is augmented by this food deficiency In some instances however it is known that the anemia precedes the dysphagia and furthermore when the difficulty in swallowing is controlled by the passage of esophageal bougies and a normal diet taken there may be no improvement in the anemia or it will disappear very slowly unless iron is added in therapeutic doses It seems likely that the causes of the anemia are those recognized as active in the etiology of idiopathic hypochromic anemia and that the mechanism of the dysphagia must remain a matter for conjecture until additional information is obtained regarding it

Symptoms and Signs—The symptoms of anemia vague indigestion general weakness and ease of fatigue usually follow the development of the dysphagia but in some well authenticated instances the reverse may be true Fissures at the corners of the mouth now thought to be due to riboflavin deficiency have been reported

The difficulty in swallowing usually comes on gradually but may develop suddenly when a small amount of solid food lodges at the level of the throat As a result the patient develops a fear of choking and will eat with amazing slowness and finally subsist entirely on an inadequate diet of semi solid or liquid food The dysphagia is much worse if the patient is obliged to dine in public and this is always avoided if possible One of my patients with the syndrome when forced by

had a hypochromic anemia associated with bleeding hemorrhoids and with this there was koilonychia Both the anemia and the koilonychia disappeared completely on treatment with iron on two occasions and there was a recurrence of the condition seven years after the patient was first treated Koilonychia may occur in very rare instances in pernicious anemia (82) although I have never seen a case It is reasonable to expect that occasionally there would be such an association because in a few patients with pernicious anemia there is also an associated iron deficiency Faber (83) did not observe koilonychia in 10 infants seven to 24 months of age with an iron deficiency anemia although in a few cases it is said to have been present since early childhood and a family incidence has been reported (84 85 86 87 88)

Other Physical Signs —The edge of the liver and spleen may be palpable in a small number of patients but less commonly in my experience than it has been in that of other observers These organs are never grossly enlarged In an occasional patient there may be slight pitting edema but if this is pronounced some other complication should be sought as an explanation of this The heart may be borderline in size and soft systolic apical (hemic) murmur is commonly present Pelvic examination should always be done as an appreciable number of these patients have benign tumors of the uterus which provide the basis for the chronic loss of blood

Blood Examination —The features are the typical ones of a microcytic hypochromic anemia with a mean corpuscular volume below 86 cubic microns and a mean corpuscular hemoglobin concentration less than 30 per cent The color index is below 1 0 and often is in the vicinity of 0 6 to 0 8 In 90 per cent of the cases reported by Wintrobe and Beebe (74) the red blood cells numbered between 3 000 000 and 5 150 000 per cubic millimeter and in 74 per cent the hemoglobin was 6 to 10 grams (38 per cent to 64 per cent on the basis of 15 6 grams equal 100 per cent)

Gastric Analysis —In about three fourths of the patients there is a complete absence of free hydrochloric acid in the gastric juice following the injection of histamine and in the remainder there is always a hypochlorhydria It has not been established as it is reasonably assumed in pernicious anemia that the achlorhydria when present has been so from birth In those patients who have this gastric change it usually persists despite the fact that the anemia disappears with iron therapy Perhaps one of the important reasons why such patients have a tendency to relapse is that the achlorhydria remains and therefore there is constantly a subnormal absorption of iron

The Plummer Vinson Syndrome —The association of dysphagia superficial glossitis and a hypochromic anemia which responds to iron therapy has in recent years been regarded as a clinical entity which in this

ened from an average length of about 50 days to 35 days after the initial blood withdrawal Following subsequent phlebotomies treatment with iron had progressively less effect on the recovery period From these observations it could be concluded contrary to what most hematologists thought previously that even the loss of a moderate amount of blood in a healthy person requires some time for replacement and this can be expedited by the administration of iron It should be emphasized however that with the removal of approximately one pint of blood the reduction of hemoglobin is within the limits of normal and that symptoms due to the lowering would not be produced Furthermore the difference between the rate of regeneration with iron and of that without it while measurable and interesting from a scientific standpoint is probably not of great practical clinical importance It is the long continued loss of blood or chronic hemorrhage which is more likely to deplete the iron stores of the body thereby creating a condition which is responsive to the administration of iron

Having been convinced that a condition of iron deficiency exists in the body satisfactory results are then almost always accomplished when iron is administered in adequate dosage The occasional exceptions to this statement will be discussed below The preparation of choice is ferrous sulphate in enteric coated tablets given before meals in doses of 0 3 to 0 6 gram three times daily The ferrous salt is advised because it is generally accepted that all iron is absorbed in the ferrous state and therefore this form is more readily absorbed than the trivalent (ferric) preparations

There is abundant evidence to indicate that the ferrous salts (divalent iron) are superior to ferric iron in the treatment of the iron deficiency anemias (92 93 94) Experimental studies on animals (95 96) however have not been in accord with the observations on man for in the former there does not seem to be any particular difference in the superiority of one form of iron over any other on the basis of absorption An explanation of this difference in the behavior of man and experimental animals with respect to iron absorption has been discovered by the experimental observations of Moore and his associates (96) in their studies utilizing radioactive iron They found that in human subjects the ferrous iron appeared in the circulating erythrocytes in a shorter time than the ferric form whereas in dogs it was not possible to demonstrate a difference in the time of appearance of the two forms of iron in the circulating blood There appears to be however a sound reason for the preference of ferrous iron in the treatment of the hypochromic anemia in man

Rarely in my experience has ferrous sulphate given in the dosage and manner suggested caused gastro intestinal irritation If this does occur the medication may be given after meals or the dose reduced to 1 or

circumstances to eat in a restaurant on arrival there would have her husband call the waiter give him a generous tip and state that they would be there at least two hours which was the time necessary for her to consume a simple meal

The tendency of these patients to develop hysterical manifestations was well illustrated by this patient who was undoubtedly psychoneurotic and introspective There were two interesting factors in her case which may have played a role in this respect One was that in middle life she developed such a masculine distribution of hair of the face which was so extensive as to require shaving daily and about which she was exceedingly sensitive The other circumstance was that she had always been an ardent advocate of prohibition and had been highly intolerant of the use of alcohol in all forms She suffered intensely therefore when by the irony of fate her only son turned out to be the town drunkard

Treatment and Prognosis—The treatment of this condition may be divided into four parts namely 1 the passage of esophageal bougies to relieve the dysphagia 2 the administration of iron in full doses 3 prescribing an adequate diet and the treating of the associated vitamin deficiencies 4 investigating and treating psychic disorders which are commonly present and reassurance of the patient

Although the immediate effects of therapy are usually gratifying there is always a tendency for these patients to relapse Hence they should be kept under observation and the blood examined at intervals of at least every three months to detect the earliest reappearance of the anemia and avert further progress if possible

Treatment of the Iron Deficiency Anemias—The treatment of these anemias is a relatively simple matter if certain well established principles are kept in mind *One is that iron is only effective when there is a deficiency of this metal in the body* Hence before prescribing iron one should be convinced that this state of deficiency exists in any given patient

Striking results are not attained for example by the administration of iron to a previously healthy person who suddenly suffers from the loss of blood by acute hemorrhage Usually there is sufficient iron stored in the body to accomplish regeneration of the blood to normal without the addition of iron supplements to the oral intake Recently however observations of interest in this connection have been made by Fowler and Barer (*91*) who studied the regeneration of hemoglobin in persons who had served as blood donors After an average withdrawal of 555 cc the mean decline of hemoglobin in 200 donors was 2 3 grams per 100 cc Usually the predonation level was restored in less than 50 days but about 26 per cent of the subjects required more than two months to accomplish this It is slower in females than in males When 1 gram of iron and ammonium citrate was given daily the recovery period was short

and red cells there are usually gratifying evidences of improvement in the patient's general condition This becomes apparent by an increase in muscular strength endurance and sense of well being Along with these changes there is a disappearance of the pallor a better appetite and a gain in body weight The tongue if smooth and atrophic may become normal in appearance once more and in some instances it has been reported that the hydrochloric acid reappears in the gastric secretions The koilonychia gradually gives way to normal appearing finger nails and if the spleen has been enlarged it will return to a normal size

If the result from iron therapy is not satisfactory one should reinvestigate the patient's condition and be reassured that an iron deficiency is present that the medication is being given in proper amounts and if there is any question about this a trial of double dosage should be given for a week or so Other possible explanations of a failure to improve are continued bleeding which may be so excessive that iron

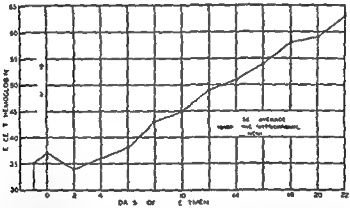

Fig 3 —The average rate of regeneration of hemoglobin following adequate iron therapy is usually about 1 per cent a day provided there is not a continued important loss of blood In the above chart the average was slightly greater than this for in the group of 7 patients the total increase was 28 per cent in 22 days following the use either of reduced iron 0 5 gram or ferrous sulfate 0.3 or 0 6 gram t i d a c In almost all patients with an iron deficient anemia there is a definite elevation of the hemoglobin following the administration of iron by the beginning of the second week of therapy In the above chart there was an increase of 8 per cent by the eighth day

medication cannot cause the blood to regenerate fast enough to compensate for the rapid loss the presence of hypothyroidism a diet inadequate in vitamins proteins or mineral salts the presence of an infection or nitrogen retention which may be observed in disturbances of the urinary tract

Adjuvants to Iron in the Treatment of Iron Deficient Anemias —Never have I observed that anything could be added to iron which would enhance its action importantly in the treatment of this type of anemia provided that initially the proper doses of the metal were employed This however is still a controversial question to some extent but prac

2 tablets daily In other words the tolerance for iron preparations should be determined If these measures fail to permit an intake of ferrous sulphate which is effective in controlling the patient s anemia ferrous gluconate in doses of 0 3 to 0 6 gram three times daily should then be tried Although this preparation is more expensive it is often better tolerated If all forms of oral medication disturb the patient intra venous saccharated oxide of iron preparation should then be given (see page 96) These preparations should not be used however until oral iron medication has been thoroughly tried and it has been demonstrated that this method cannot be employed In the many years that I have used iron preparations in large doses I cannot recall more than a few instances in which it was impossible for the patient to con tinue with it on account of untoward gastro intestinal symptoms Even in these cases it may have been purely suggestion rather than a real idiosyncrasy to the drug On the other hand during that interval on many more occasions I have had patients referred to me by practitioners with the statement that they cannot tolerate any preparation of iron only to find that they can take ferrous sulphate without difficulty if the above suggestions are followed

For infants and young children the following stable elixir may be employed

Dilute Hypophosphorus acid	0 6 cc
Ferrous Sulphate	3 0 grams
Dextrose	30 0 grams
Chloroform water to	120 0 cc

Sig —4 cc three times daily p c

This dosage provides 0 3 gram (5 grains) daily which is suitable for infants and children up to 2 years of age Twenty cc of this mixture may be given daily to children from two to six years of age and for those over six years the dose should be 24 cc daily This preparation may be given after meals in order to lessen gastro intestinal irritation Some prefer to take it in milk

Following iron therapy usually within the first week there is a slight rise in the number of reticulocytes of the circulating blood which indicates a favorable response to the medication This increase does not reach the heights following the treatment of pernicious anemia with liver extract as it rarely exceeds 10 or 12 per cent at the most and is usually in the vicinity of 6 to 8 per cent On about the eighth day after the treat ment is initiated the hemoglobin of the circulating blood begins to rise at the rate of approximately 1 per cent daily (0 16 to 0.2 grams) until the blood approaches normal limits at which time the increase is at a slower rate

With the rise in the reticulocytes and the increase in the hemoglobin

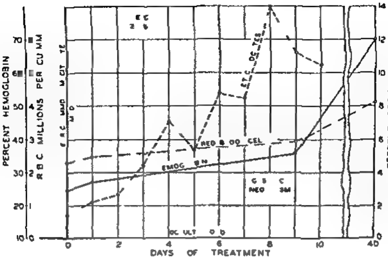

Fig 6—Treatment with iron which proved to be effective in controlling the anemia due to a bleeding gastric cancer The most important cause of anemia in malignancy involving the gastro intestinal tract is chronic hemorrhage While iron therapy merely controls one of the results of the neoplasm nevertheless it is a simple inexpensive method of restoring the blood to normal in many cases and which often contributes materially to the comfort of the patient In the above patient the hemoglobin rose from 25 per cent to 70 per cent and the red blood cell count from 2 ▮ to approximately 4 0 millions per cubic millimeter in 40 days with the use of ferric ammonium citrate daily No other form of treatment was given to combat the anemia

tically all experienced hematologists do not consider that the addition of copper secondary anemia liver extract ventriculin or liver extract produces an effect which is in any way superior to the proper use of iron alone Many drug houses furnish these expensive mixtures for the treatment of the hypochromic anemias but the therapeutic effects are probably due solely to their iron content

It is acknowledged that there is ample experimental evidence which demonstrates that rats fed exclusively on a milk diet will regenerate their hemoglobin more rapidly on a mixture of iron and copper than on iron alone This data is however of no clinical importance at least in adults for there is no indication that there is a deficiency of copper in the blood and the average diet contains from 2 to 4 milligrams of this metal Furthermore practically all of the commercial preparations of iron which are used in medicine are contaminated with copper Hence unwittingly this element is administered with all doses of iron

Some years ago we desired to perform some experiments on humans and endeavored to place them on a low copper diet With a good deal of planning and elaborate effort it was possible to devise a diet which contained only 1 milligram of copper daily In addition it was exceedingly difficult to eliminate all of the copper from the preparations of iron which we administered The additions of more copper as a therapeutic

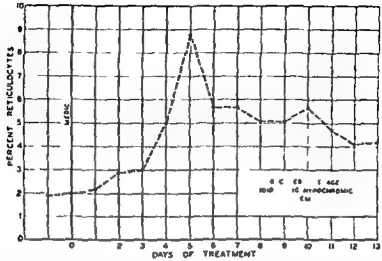

Fig 4 —Following adequate iron medication in patients with an iron deficiency anemia there is a definite reticulocyte response as indicated by a rise in the number of these cells in the circulating blood As shown above the increase begins by the fourth day following treatment reaches its peak on about the fifth to the seventh day and usually persists for between 10 to 14 days Such a response is always definite but much less than that seen in patients with pernicious anemia who receive potent antipernicious anemia medication

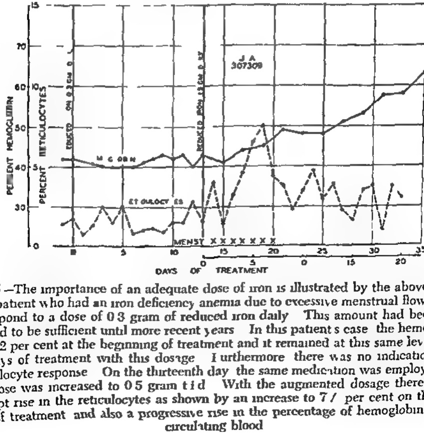

Fig 5 —The importance of an adequate dose of iron is illustrated by the above chart This patient who had an iron deficiency anemia due to excessive menstrual flow failed to respond to a dose of 0 3 gram of reduced iron daily This amount had been considered to be sufficient until more recent years In this patient s case the hemoglobin was 42 per cent at the beginning of treatment and it remained at this same level after 12 days of treatment with this dosage Furthermore there was no indication of a reticulocyte response On the thirteenth day the same medication was employed but the dose was increased to 0 5 gram t i d With the augmented dosage there was a prompt rise in the reticulocytes as shown by an increase to 7 / per cent on the fifth day of treatment and also a progressive rise in the percentage of hemoglobin in the circulating blood

should be a slight reaction the dose should then be given more slowly or the amount reduced to 40 milligrams

The medication may be given daily until the desired effect is attained (It is suggested by Brown and his associates (*102*) that the initial dose be 20 to 50 milligrams and that the daily dose be 100 to 200 milligrams until the deficiency is corrected) The following formula is suggested by these investigators to estimate approximately the total amount of iron needed to bring the blood to normal The normal hemoglobin (15 0 grams per 100 cc of blood) minus the observed hemoglobin in the patient multiplied by the factor 0 255 will give the total theoretical dosage necessary to bring the blood to normal This may be given at the rate of 100 milligrams per day For example if the observed hemoglobin is 7 5 grams thus subtracted from the normal hemoglobin gives 7 5 grams when this figure is multiplied by 0 255 it gives 1912 5 milligrams which is the total amount to be given on 15 consecutive days in doses of 100 milligrams

As injected iron in the adult is excreted normally from the body only in exceedingly small amounts the possibility arises that the ill advised injection of larger than the total suggested therapeutic dose might cause deposits of iron in the body and possibly produce hemochromatosis as is occasionally observed in patients following multiple blood transfusions (While there is clinical and experimental evidence suggesting that the intravenous injections of large amounts of iron may cause pathologic changes in the body it is unlikely that harm would result from the injections of iron in doses suggested by Brown *et al* (*102*) when given to patients with an iron deficiency anemia) *Excessive dosage however is to be avoided and the preparation should never be administered to patients unless an iron deficiency exists*

The indications for the administration of iron intravenously are few This is because in almost all instances of an iron deficiency the response is satisfactory with oral therapy Parenteral administration should never be employed until it has been demonstrated that the oral type of medication is ineffective If it can be shown that patients with an iron deficiency anemia do not adsorb iron efficiently as in sprue idiopathic steatorrhea following intestinal operations or for unknown reasons the parental use of iron is then indicated I have incomplete observations on one patient with an iron deficiency anemia who appeared to have had a resistance to iron medication but I could not be certain that the preparation was being taken a point which should always be kept in mind In an occasional patient there have been complaints that iron could not be tolerated but when decreased dosage is employed the medication given in enteric coated tablets and after meals this rarely occurs Certainly intravenous iron is not to be recommended in patients who can respond adequately to the oral type of medication

measure, to iron medication at least in adults is unwarranted by clinical experience. On the other hand it is claimed by some that the addition of copper to the diet of anemic infants (*97*) is advantageous but this observation has not been confirmed by other observers (*98*)

Intravenous Iron Preparations.—Until recent years there have been no satisfactory preparations of iron suitable for intravenous use which could produce a therapeutic result without causing unpleasant and sometimes serious complaints The preparations employed were colloidal ferric oxide and ferric hydroxide ferrous citrate ferrous gluconate *ferrous ascorbate* and others. *Although* all iron preparations had a tendency to produce untoward symptoms when given intravenously the colloidal preparations when injected were more likely to cause nausea and vomiting abdominal and lower back pain nasal stuffiness lacrimation headache swelling and flushing of the face paresthesia and in some patients a fall in systolic pressure substernal pain and a sense of impending death It was established however by the earlier observations that the injected iron was converted almost quantatively to hemoglobin and that with proper doses there was a prompt reticulocyte rise and a *maximal rate of hemoglobin increase*

The presence of these objectional symptoms along with the fact that oral preparations of iron were satisfactory in most instances properly discouraged the use of the intravenous preparations until recently. In the past few years it has been demonstrated by a number of British investigators including Nissim (*99*) Slack and Wilkinson (*100*) and Davidson and Cirdwood (*101*) and others that saccharated oxide of iron can be given safely and effectively in therapeutic doses More recently Brown Moore Reynafarje and Smith (*102*) have treated a group of patients with hypochromic anemia by *means of the intravenous injection of* saccharated iron oxide and report that excellent therapeutic results were obtained They stated that the blood was restored to normal with a *maximum hemoglobin regeneration averaging a daily rise of 0 177 gram* per 100 cc associated with a reticulocyte rise of 15 per cent or more in most of the patients and that within a few days there was an increase of appetite and diminution in weakness)

Reactions were infrequent and mild The preparation employed was saccharated oxide of iron containing 100 milligrams in 5 cc It was *prepared by Smith* Kline and French Wm S Merrell Company and Sharp and Dohme Inc A British preparation which has been used extensively in England is Ferrivenin, (Bentgers Limited) in which a 5 cc ampule also contains 100 milligrams of iron The material does not ordinarily cause thromboses of the veins but if any is accidentally *injected outside the vein a painful induration may occur* It is usually dispensed in 5 cc ampules containing 100 milligrams of iron in 5 cc of fluid and this amount may be administered in 30 seconds If there

Ordinarily it is not necessary to administer dilute hydrochloric acid although many patients with iron deficiency anemia have a hypochlorhydria or an achlorhydria This is because the gastro intestinal complaints usually subside completely without other therapy than iron In a few patients however there will be continued complaints referable to the abdomen If additional studies show no organic reason for this such as cholecystitis or cholelithiasis or pathologic lesions elsewhere then *dilute* hydrochloric acid U S P may be given in doses of 4 cc in a full glass of water with meals In some instances the patients have reported that the symptoms have been relieved

Rarely are blood transfusions indicated because the results from iron therapy are so prompt and satisfactory They should be given if the hemoglobin level is so low as to endanger life which it rarely is and if the clinical picture is complicated by the presence of any severe acute infection such as lobar pneumonia In some instances such as an emergency operation transfusions are justifiable when this procedure cannot be delayed a sufficient period for the blood to return to normal with iron therapy Occasionally it may be advisable to administer one or two transfusions in order to expedite the patient s recovery and shorten the period of hospitalization

Prognosis —This varies with the type of iron deficiency anemia which is present In the nutritional anemia of children in chlorosis and idiopathic hypochromic anemia of women the effect of iron is prompt and all that is to be desired It should always be remembered however that these conditions are characterized by an ever present tendency to recur although in the case of female adults this usually disappears after the menopause Iron medication should be continued for long periods of time and the patients observed until the periods of rapid growth or in the case of adolescent and adult women until there are no longer excessive demands for iron such as those associated with menstruation pregnancy and lactation

In the variety of anemia due to chronic hemorrhage the outlook is of course dependent on the underlying cause of the bleeding The anemia *is always amenable to iron therapy provided the loss of blood can be* controlled Even in cases of blood loss due to malignancy as in carcinoma of the stomach the anemia may be at least partly corrected by iron medication and the patient thereby benefited temporarily

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This is because as stated by Brown *et al* (*102*) reactions even though mild and infrequent will prove troublesome daily injections for 10 to 14 days *will often be inconvenient* and the cost to the patient is likely to be considerably greater than for oral therapy

Toxicity of Ferrous Sulphate—Ferrous sulphate is usually considered to be a harmless drug and there is no indication that it has toxic effects when given orally in therapeutic doses Recently however, Smith, Jones and Cochran (*103*) have summarized the literature dealing with the dangerous effects of large doses and reported a fatal case observed by them Their patient was a 17 month old girl who ingested about 20 enteric coated ferrous sulphate tablets which she obtained from the pocket of a coat hanging on a door knob Four hours later there was vomiting and diarrhea and seven hours after the tablets had been taken *there was a pronounced cyanosis which was attributed to methemoglobin* formation It did not respond to oxygen but did promptly to methylene blue The patient displayed all of the manifestations of severe shock and died about 11 hours after the iron had been ingested

In all patients who had poisonous effects from the drug the doses have been disproportionately large Usually the patients have been children but one adult 26 years old is reported by Foucar Gordon, and Kaye (*104*) who died following the ingestion of *one fourth pound* of ferrous sulphate It is recommended by Smith Jones and Cochran (*103*) that first aid in the home should consist of feeding raw eggs and milk so that the protein could absorb the iron Hospitalization should be prompt and apomorphine employed in the early cases if necessary to produce vomiting BAL is not indicated because of the possibility that the combination of this material with certain metals may enhance their toxicity If methemoglobinemia is present, it is recommended by Finch (*105*) *that methylene blue be given intravenously in a dose varying from a fraction of milligram to 10 milligrams per kilo of body weight* Whole blood should be administered if the patient is in shock

Secondary Anemia" Liver Extract and Other Forms of Therapy—In *1930* Whipple and his *associates* (*106*) *reported* that *the portion of liver* which was precipitated by 70 per cent alcohol the so called secondary anemia fraction was effective in accelerating hemoglobin regeneration in dogs made anemic by repeated bleeding He did not believe that the effect was produced by the iron content of the fraction Whatever may have been the experimental results in dogs suffering from an anemia as the result of bleeding there is no indication derived from the study of patients that this fraction is of therapeutic value in anemia due to hemorrhage

Furthermore, there is no proof in patients that the addition of cobalt calcium amino acids or any of the vitamins produce any better effects than the administration of iron plus a general well balanced diet

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CHAPTER IV

ANEMIAS OF PREGNANCY

Definition —*A true anemia of pregnancy may be defined as one due primarily to the gravid state in which the hemoglobin is less than 10 grams per 100 cc or the red blood cell count is below 3 5 millions per cubic millimeter or both changes are present* In my experience in addition it may be said that the size of the red blood cells and their hemoglobin content remain within normal limits in the physiologic anemia of pregnancy which is a dilution effect and cannot be regarded as abnormal

Classification —*The anemias of pregnancy may be classified under the* following headings

1 Physiological anemia
2 Microcytic hypochromic anemia due to iron deficiency
3 Macrocytic anemia
4 Anemias incidentally associated with the gravid state

The classification given by Whitby and Britton (*1*) is as follows

1 Hypochromic anemias
 (a) Idiopathic hypochromic anemia complicated by pregnancy
 (b) Hypochromic anemia induced by pregnancy
2 Megaloblastic anemias
 (a) Megaloblastic anemia complicated by pregnancy
 (b) Megaloblastic anemia induced by pregnancy
3 Hypoplastic anemia
4 Hemolytic anemias
 Acute hemolytic anemia of Lederer
5 Secondary anemia complicated by anemia e g streptococcal and staphylococcal septicemia malignant disease leukemia nephritis hemolytic icterus, hookworm infection malaria syphilis

History —It is usually stated that the earliest description of the anemia of pregnancy is that of Nasse (2) in 1835 Osler especially emphasizes however the contributions of Channing (1842) Lembert (1853) and Gusserow (1871) *as being of more importance* Furthermore he reminds us that several of Biermer's early cases of *Progressive Pernicious Anemia* described in 1872 were in pregnant women

The early report of Channing well deserves a prominent place in the historical development of our knowledge of the anemia of pregnancy This observer the Professor of Obstetrics and Dean of the Harvard Medical School published his paper in the *New England Quarterly Review of Medicine and Surgery* for October 1842 (3) He presented a number of case histories of women having anemia not associated with childbirth either due to uterine hemorrhage or other causes In one young woman he attributed the condition undoubtedly correctly to excessive phlebotomy as she had been bled *96 times in 2½ years* Nine of his cases however were either associated with pregnancy or the puerperal state In each instance the condition terminated fatally He minimizes rather vaguely the importance of excessive loss of blood as a cause of such a condition mainly because the patient in one instance ' was seen to live for 18 days without flowing Hence he became convinced that there was some less obvious and less appreciable cause of the phenomena " It is of interest that even at that early date he suggested that blood transfusions might be a satisfactory form of treatment although there is no record that he gave one

One of the earliest references to the anemia of pregnancy was in 1874 by H N Bennett (4) in which he defines such an anemia as a morbid state resulting only from the process of reproduction He called attention to a peculiar inflammatory condition of the buccal and lingual mucous membranes which does not develop until after delivery and in some instances not until after lactation begins In his opinion the sore mouth with the gastric disturbances constituted the chief evidences of the morbid process He considers that such an anemia should be regarded as a transition from the physiological anemia of pregnancy to a pathological state

One of the earlier descriptions of the physiological anemia of pregnancy was that of Spiegelberg in 1872 (5 6) who stated that it is an old doctrine that as the quantity of blood increases that a plethora sets in during pregnancy indeed I have shown that such an augmentation takes place in dogs during pregnancy and a similar change probably occurs in a healthy woman It is obvious that the important concept of the physiological anemia of pregnancy had also been clear in the mind of Willcocks (7) for he wrote in 1881 that after examining the red blood cell count and hemoglobin content of the blood of 26 cases of pregnancy that it was possible to differentiate between chlorosis and pregnancy anemia He concluded that the condition of the blood in healthy pregnant women does not constitute a true anemia but is accounted for by the large increase of the water of the plasma "

In more recent years numerous attempts have been made to establish the occurrence and estimate the increase in blood volume in pregnancy Among those who have contributed information of value in this direction

have been Miller Keith and Rowntree (*8*) and Schoenholtz (*9*) A review of the literature dealing with the physiological anemia of pregnancy is given by Dieckmann and Wegner (*10*)

In 1918 Schmidt (*11*) described four cases of pernicious anemia of pregnancy in detail and included excellent blood studies Of greatest importance is his reference to the beneficial effects of blood transfusion in each case To Schmidt therefore should be given credit for having been one of the earliest to emphasize the great value of this form of therapy in these patients He states " Too much emphasis cannot be put upon the importance of the life saving effects of the transfusion of blood in these patients The rapidity with which the anemia can develop is surprising and the mortality reported is appalling It is therefore urged that transfusion should not be used as a measure of last resort but early, as soon as the diagnosis can be made " The difference between this type of anemia and true pernicious anemia was also emphasized by Schmidt He called attention to the fact that hydrochloric acid may be present in the gastric secretions that leukocytosis is frequent that there are no remissions and that spinal cord symptoms are absent

Osler s classical paper on "The Severe Anemias of Pregnancy and the Postpartum State" which appeared in the *British Medical Journal* during 1919 (*12*) did much to emphasize the importance of these anemias and also contains a summary of the then existing literature Such anemias were divided by Osler into four main groups as follows

I Anemia from postpartum hemorrhage
II The severe anemia of pregnancy
III Postpartum anemia
IV The acute anemia of postpartum sepsis

Groups I and IV are due to well recognized causes It is now thought that groups II and III are attributable to the same mechanism and differ only in that they appear at different times with reference to the pregnancy It is my present opinion that these types of anemia may possibly be due to a diminished intake of protein especially the animal variety which is of high biologic quality This is in accord with the theory first advanced by Bethell (*13*)

Of special interest has been the development of our knowledge in recent years of the macrocytic anemia of pregnancy in the native women of India In 1927 McSwiney (*14*) observed 43 cases of macrocytic anemia in 2544 pregnant women in Calcutta an incidence of 1 69 per cent In the same year Balfour (*15*) reported 150 cases seen in Bombay over a period of 1½ years Lucy Wills (*16 17*) has also directed attention to this type of anemia with excellent therapeutic studies It is recognized that in India a similar macrocytic anemia also occurs in non pregnant women and in men

In 1918 as previously stated Schmidt reported the beneficial effects of blood transfusions (*11*) and in 1926 Reist (*18*) observed two cases of this type of anemia treated successfully with blood transfusions and collected reports of 14 similar ones in the literature The prediction that many cases of anemia would be successfully managed by the use of a liver diet was made by Murdock (*19*) The earliest cases treated by such a diet were those of Deschamps and Froyez (*20*) Audebert and Fabre (*21*) Brault (*22*) and Peterson Field and Morgan (*23*) The latter concluded that liver seemed to exert a specific influence in this condition similar to that exhibited in primary pernicious anemia

The first patient with the macrocytic anemia of pregnancy treated successfully with desiccated hog stomach was reported by Wilkinson (*24*)

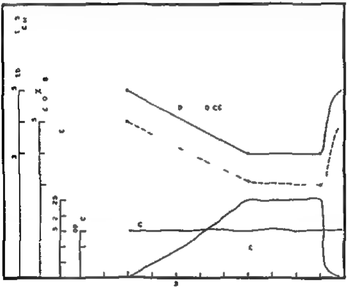

Fig 7 —The above diagram shows that from almost the beginning of pregnancy there is a gradual increase in the blood plasma volume which reaches its maximum of about 25 per cent at the sixth month During the remainder of pregnancy it remains constant and then rapidly returns to normal immediately following delivery As a result of this increase in plasma volume there is dilution of the hemoglobin and red blood cells which produces the physiologic anemia of pregnancy As a result of the maximum dilution of normal values for the hemoglobin and red blood cell count they may be reduced to as much as 10 grams (64%) and 3 5 millions per cubic millimeter respectively If the levels are below either one of these figures then it is known that the anemia is more than physiologic When only a physiologic anemia is present the color index remains within the vicinity of 1 0 and the mean corpuscular volume and mean corpuscular hemoglobin concentration are also normal

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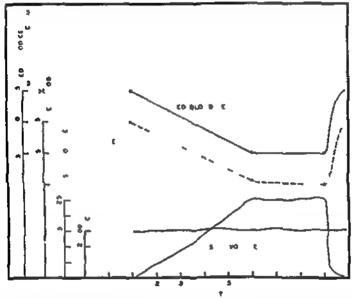

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The Physiological Anemia of Pregnancy—It has long been known that in all pregnant women there is a progressive decline in the number of

red blood cells and hemoglobin concentration of the circulating blood. This begins early in the pregnant state and reaches its maximum at about the sixth month. Thereafter there is no change until about two weeks after delivery at which time the blood returns to normal. These changes are associated with an increase in the plasma volume of the circulating blood which decreases the concentration of both the erythrocytes and leukocytes. There is apparently a compensatory increase in the number of white blood cells which accounts for their presence in normal numbers, but this does not occur in the case of the red blood cells. At least if there is a compensatory increase in the rate of formation of erythrocytes it is not sufficient in extent to cause the red blood cell count to return to normal.

TABLE V

	R.B.C. (Per Cu. Mm.) Millions	Hb.	C.I.	M.C.V. (Cu. Microns)
Minimal Normal in Non-Pregnant Women	4.13	78		
Lowest Possible Change Due to Hydremia (Calculated)	3.53	67		
Changes Actually Observed in Pregnancy				
Month of Pregnancy				
3 Months	4.12	73	0.96	92.5
4 Months	4.07	71	0.94	92.4
5 Months	4.04	70	0.93	91.3
6 Months	3.86	70	0.97	93.8
7 Months	4.04	71	0.95	91.1
8 Months	4.07	71	0.94	91.4
9 Months	4.18	71	0.92	90.9

TABLE V.—The above data illustrate the normal physiological anemia of pregnancy due to hydremia with the resultant dilution of the red blood cells. It is estimated that the lowest minimal red blood cell count in normal women is 4.13 per cubic millimeter and the lowest hemoglobin is 78 per cent (Bethell). If a woman with such a count attains the greatest possible dilution, that is, 26 per cent, then the lowest calculated change in the red blood cell count would be 3.53 cells per cubic millimeter and the lowest hemoglobin percentage 67 per cent. The figures given are those actually observed in a pregnant woman from the third to the ninth month. It should be noted that in addition to the reduction in the red blood cells and the hemoglobin the blood otherwise remained nromal as indicated by the normal color index and cell size.

In 1934 Dieckmann and Wegner (*10*) made a valuable blood volume study in pregnancy and reviewed the literature on the subject. Their conclusions, in general, are in accord with those given in the above paragraph. These authors, while they observed that repeated findings on the same individual checked closely, were aware that the Keith-Rowntree method which they used (*25*) was liable to definite errors. Blood volume studies in normal pregnant women have been made by Thompson and his associates (*26*) who employed the method introduced

by Gregersen, Gibson and Stead (27) and adapted to clinical use by Gibson and Evans (28). They conclude that there is a definite increase *in the cell volume during the latter months of pregnancy, but that this is* distinctly less than the augmentation of the plasma volume. This disproportionate increase appears to be primarily accountable for the phenomenon of hydration. They conclude that unquestionably the blood is more dilute in pregnancy than in the non-gravid state, but the causal factor or accounting for the increase in blood volume has not been demonstrated.

Several years ago Bethell (13) made a careful study of the changes which occurred normally in the blood of pregnant women as a preliminary survey to the study of the anemias of pregnancy. The details of these changes are shown in Table IV. In brief, it may be said that the lower limit of the normal red blood cell count during the course of pregnancy is regarded as 3.5 million per cubic millimeter, and of the hemoglobin 10 grams per cc. of blood (64% of a normal assumed to be

TABLE VI

CALCULATED EFFECT OF 25% DILUTION OF THE BLOOD OF NORMAL WOMEN

	Red Blood Cells	*Hematocrit (Per Cent)*	*Plasma Volume (Cc.)*	*Hemoglobin (Per Cent)*
Average Normal	4,800,000	42.5	3000	90 (14.2 Gm.)
25% Dilution	4,200,000	37.0	3750	80 (12.6 Gm.)
Low Normal	4,300,000	38.0	3000	80 (12.6 Gm.)
25% Dilution	3,700,000	32.7	3750	70 (11.[illegible] Gm.)

TABLE VI.—Calculations to illustrate the effect of the dilution effect on the hemoglobin and red blood cell count in pregnancy. It is estimated that the maximum dilution due to this factor occurs at about the sixth month of pregnancy and continues at this level until term. The table shows that if the average red blood cell count and hemoglobin percentage were normal before pregnancy, then the maximum dilution would produce a reduction in the red blood cell count to 4.[illegible] millions per cubic millimeter and a hemoglobin percentage of 80 (12.6 grams). On the other hand, if the red blood cell count [illegible] somewhat reduced (4.3 millions per cubic millimeter) and the hemoglobin also is at the lower limit of normal (80 per cent, 12.6 grams), then a 25 per cent dilution will result in values which are considerably below normal, namely, a red blood cell count of 3.7 millions per cubic millimeter, and a hemoglobin percentage of 70 (11.0 grams).

15.6 grams per 100 cc. of blood). Any determinations which fall below these standards during the course of pregnancy are indicative of a pathological anemia of pregnancy. These observations are based upon innumerable examinations of the blood of normal women of the child-bearing age, blood studies in many normal women during and following pregnancy, and certain clinical and experimental studies on the effect of the dilution of the hemoglobin and the erythrocyte concentration.

As shown by the standard values for blood (29), in the last trimester of pregnancy the following findings which are below the standards for normal non-pregnant women may be found as evidence of the physiologic

anemia of pregnancy and hence would be regarded as normal red blood cell count 3 5 millions per cubic millimeter hemoglobin 10 2 grams per 100 cc hematocrit 37 per cent mean corpuscular hemoglobin concentration 31 per cent mean corpuscular hemoglobin 28 micrograms, and mean corpuscular volume 77 per cent I am in accord with these figures as given with the important exception that in my experience the *red blood cells in patients with the physiologic anemia of pregnancy have always been normal in size (86 to 96 cubic microns) A definite change in the size of the erythrocytes so that they are larger or smaller than normal may be the most important finding which differentiates the physiologic from an abnormal anemia of pregnancy*

As will be discussed later *it should be emphasized that the increase in* the plasma volume during pregnancy causes a dilution of the red blood cells and hemoglobin During pregnancy this serves to accentuate any

TABLE VII

INCIDENCE AND TYPE OF ANEMIA OF PREGNANCY

	No	*Per Cent*	
Total Cases Studied	158	100	
Cases with Iron Deficiency Anemia	42	27	Hb Below 10 0 Grams Per 100 cc M C Hb Below 26yy (C I below 0 9)
Cases with Diet Deficiency Anemia	24	15	R B C Below 3 5 Millions Per c mm M C V Above 97 c microns (C I above 1 1)
Cases with Mixed Deficiency Anemia	19	12	Features of Both Above Types Are Present
Total Incidence of Anemia	85	54	

TABLE VII —The results of a study of the blood in 158 supposedly normal pregnant women observed routinely as they came to our obstetrical outpatient department None of them had any special complaints and regarded themselves as in good health In separating the patients with a physiological anemia of pregnancy from those with an abnormal anemia the lowest level of normal of the red blood cell count was regarded as 3 5 millions per cubic millimeter and the minimum normal hemoglobin level as 10 grams per 100 cc or [illegible] per cent With these criteria as guides it was found that 85 women or 54 per cent of 158 women had an abnormal anemia of pregnancy Twenty seven per cent had an iron deficiency type and 15 per cent had a macrocytic anemia which Bethell considers is associated with an inadequate *intake of protein In 12 per cent of the patients there was hypochromia of the erythrocytes* and also [illegible] macrocytosis It was considered therefore that this was a mixed anemia due [illegible] a deficiency of iron and also of protein Many of these women came from families of a lower economic status and hence the food supply was probably not adequate The relatively high incidence of such anemia was unexpected It cannot be attributed entirely to inability to secure a proper diet as [illegible] similar study in a prosperous farming region of Michigan showed an incidence of 26 per cent

(Bethell Gardiner and MacKinnon Courtesy *Annals of Internal Medicine*)

pre existing anemia and make more apparent the actual reduction in the hemoglobin and red blood cells This factor alone may have the effect therefore of converting an exceedingly mild anemia to one of moderate severity during pregnancy

Incidence of the Anemias of Pregnancy—Several years ago studies at the Simpson Memorial Institute under the direction of Bethell and his associates (30) showed that approximately 54 per cent of all supposedly healthy pregnant women who came to our obstetrical out patient department had a pathological anemia Such an anemia is one associated with a hemoglobin of less than 10 grams per 100 cc (64 per cent) or the red blood cell count of 3 5 per cubic millimeters or less or both changes prevail The figures just given are the lowest levels that can result from the approximate 26 per cent increase in the blood plasma which accounts for the dilution effect and its production of the physiologic anemia of pregnancy

Additional observations made in Hillsdale and Allegan counties in Michigan which are essentially rural in character showed that in these areas a pathological anemia was present in 30 per cent of all cases If it is true that at any given time there are 2 500 000 pregnant women in the United States and if it can be assumed that 30 per cent of them have a pathological anemia of pregnancy it would mean that 750 000 women are suffering from an easily controlled condition which if untreated is a hazard to both mother and child If these figures are applied to the world at large especially in those regions in which there is frank under nutrition the enormity of the problem is obvious

In recent years the incidence of anemia as a complication of pregnancy appears to have been diminishing in the British Isles according to Scott and Govan (31) In proof of this they cite the observations of Fullerton Mair and Unsworth (32) in which they state that in 1944 only 3 9 per cent of pregnant women in Aberdeen of the hospital class have an anemia This represents a rapid diminution in the number of cases since 1935 (33) In Glasgow however it was found by Scott and Govan (31) that anemia was a common complication of pregnancy in the years 1946–47 These conclusions were based on a survey of 4595 women at the antenatal clinic of the Glasgow Royal Maternity and the Women s Hospitals Using 10 36 grams per cent as the lowest limit of normal they found that 20 1 per cent of all the pregnant women examined were either anemic or became anemic during the course of pregnancy

Of the two main pathological anemias of pregnancy the iron deficiency variety is more common In the 54 per cent of patients observed at the out patient department of the University Hospital with an anemia it was found that 27 per cent had the iron deficiency type and 15 per cent the macrocytic variety In 12 per cent it was considered that both etiological factors were active

Iron Deficiency Anemia of Pregnancy—During pregnancy there is a notable increase in the iron requirements due to the fact that there are added demands which may be classified under three main headings There is an increase in the iron requirement in pregnancy in order

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pre existing anemia and make more apparent the actual reduction in the hemoglobin and red blood cells This factor alone may have the effect therefore of converting an exceedingly mild anemia to one of moderate severity during pregnancy

this question it seems that the following statement is a fair presentation of the situation The requirements of normal pregnancy including the bleeding at delivery is probably two or three times greater than the loss by normal menstruation over a corresponding interval

It is stated by Hynes (36) from information based on the studies of Davidson and Fullerton (37) that a pregnant woman contributes 400 milligrams of iron to the fetus and 150 milligrams to the placenta and uterus There is an estimated blood loss in parturition of about 500 cc which accounts for a further loss of 175 milligrams making a total of 725 milligrams The greater part of this added iron requirement is toward the latter part of pregnancy when the fetus is laying down most of its iron stores but for convenience this can be expressed as an average need of 2.7 milligrams daily When this is added to the daily iron requirements of normal non pregnant women as estimated from biliary and urinary excretion which equals 1.1 milligrams the total iron daily requirement of women throughout pregnancy may be estimated to be 3.8 milligrams which is almost twice the needs (2.1 milligrams) of a normal woman who is menstruating regularly

If it is not possible to retain a sufficient quantity of food iron the maternal organism must necessarily depend upon the pre existing stores of the metal for the satisfaction of fetal requirements and the prevention of maternal anemia Factors which play important roles in the depletion of such stores include an habitual low dietary intake gastro intestinal disorders hypermenorrhea and frequently repeated pregnancies It should be emphasized therefore that probably the most important factors in the etiology of the iron deficiency anemias of pregnancy are 1 the increased iron requirement which makes necessary the use of maternal iron stores and 2 often a slight iron deficiency anemia which is present before pregnancy and is an *indication that the iron reserves even before pregnancy are inadequate*

Another factor which must be considered is the accentuation of an existing anemia as a result of the increase in the plasma volume which is always present during pregnancy For example it is known that a maximum blood dilution of about 26 per cent occurs at the sixth month of pregnancy If the hemoglobin before pregnancy were 70 per cent this factor alone would reduce it to approximately 58 per cent The *most acceptable view concerning the factor of greatest importance of the iron deficiency anemias of pregnancy is therefore that some degree of anemia has existed prior to pregnancy and that this becomes intensified as a result of the physiological hydremia*

Regardless of how such an anemia is produced there is no difference of opinion concerning the fact that it is attributable to a deficiency of available iron This is clearly established by the observation that the administration of adequate doses of this metal will promptly restore the

1 To supply fetal needs including the formation of hemoglobin and tissue cytochrome and to create reserves of the metal in the embryo
2 To form additional erythrocytes in an attempt to compensate at least partially for the anemia due to the plasma volume increase
3 To meet the requirements due to the formation of additional maternal tissue

Another factor which is of possible importance in the anemias of pregnancy is the presence of a hypochlorhydria or achlorhydria which is not infrequently associated with the gravid state It is known that such a change impairs the normal absorption of iron from the gastro intestinal tract

In 1942 Balfour and his associates (*34*) as a result of a small number of tagged iron absorption studies in a limited group of pregnant women found that they absorbed about two to ten times as much iron as non pregnant persons In 1947 Hahn *et al* made further studies (35) to determine the effects of various factors on the absorption of iron by the pregnant woman In 1951 a more extensive study utilizing the radio active isotope Fe 59 was made in a group of 466 women most of whom had uncomplicated courses were non anemic and would be considered healthy pregnant women They found that with an uptake of 8 per cent in their subjects following a dose containing 120 milligrams of elemental iron about 10 milligrams would enter the circulation This *dose is the amount of such iron which is contained in 0 325 gram of* desiccated ferrous sulphate It is a larger amount of iron than is con tained in the 5 grain tablets of crystalline ferrous sulphate or 3 grain tablets of desiccated ferrous sulphate Both of these are commonly given in pregnancy and would not represent optimal dosage according to these observations For example both of the latter tablets would contain 65 milligrams of elemental iron rather than the optimal dose of 120 milligrams

As gestation progressed it was found that the uptake of iron increased so that at 30 weeks gestation and over three or four times as much iron was absorbed as during the period before the fifteenth week of preg nancy At birth about 10 per cent of the radioactive iron which was administered to the mother was found in the red blood cells of the infant The observers state that if one were dealing with a group of pregnant women who had hypochromic anemia due to an iron deficiency one would expect to find a relationship between the hemoglobin level and iron uptake That is the lower the hemoglobin level and hence the greater the deficiency of iron the greater would be the iron uptake

Although pregnancy increases the demand for iron there is some conservation of the metal as the result of the absence of menstrual periods Although there is not an entirely uniform opinion in regard to

this question it seems that the following statement is a fair presentation of the situation. The requirements of normal pregnancy including the bleeding at delivery is probably two or three times greater than the loss by normal menstruation over a corresponding interval.

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Regardless of how such an anemia is produced there is no difference of opinion concerning the fact that it is attributable to a deficiency of available iron. This is clearly established by the observation that the administration of adequate doses of this metal will promptly restore the

blood to normal for pregnant women and give assurance that the infant will be born with adequate iron reserves

The relation of the iron intake in the food and the existence of a hypochromic anemia has been made clear by the studies of Bethell and Blecha (38) of 234 patients during pregnancies They found that when the daily dietary intake of iron in pregnant women is 16 milligrams or more hypochromic anemia is not present On the other hand, when the intake is less than 8 milligrams daily hypochromic anemia appears in almost 40 per cent of the patients

The Blood in Patients with Iron Deficiency Anemia of Pregnancy — The blood in this condition shows the typical changes observed in non pregnant patients with a hypochromic anemia Most frequently the red blood cell count is between 3 0 and 4 0 millions and the hemoglobin from 8 grams to 10 grams per 100 cc of blood (51 to 64 per cent) The red blood cells may be normal or below normal in size In some instances the anemia may be due to two etiological factors one a deficiency of iron which reduces the hemoglobin content of the cells In such patients with a combined anemia their hemoglobin would be below 10 grams per 100 cc of blood (64 per cent) and the red blood cell count 3 5 millions per cubic millimeter or less Such a patient would commonly have a hypochromic normochromic or macrocytic anemia

It is emphasized by Klopper and Ventura (39) that patients with an iron deficiency anemia of pregnancy show a definite pattern of change as follows the characteristic hematological picture is present namely evidences of a hypochromic microcytic anemia the serum iron falls to a low level the iron binding capacity of the serum protein is considerably increased the level of serum copper rises above normal limits the amount of free erythrocyte protoporphyrin is raised as there is insufficient iron to combine with all of the available protoporphyrin All of these patients responded to the intravenous injection of iron In an additional study (*40*) of the serum iron in pregnant women after the metal had been given orally and intravenously it was found that the pregnant woman had a greater power to absorb and transport iron This was interpreted as evidence in support of the thesis that a state of latent iron deficiency exists in pregnancy

The Macrocytic Anemia of Pregnancy —Macrocytic anemia of pregnancy has been observed over a period of many years and because of its resemblance to true Addisonian pernicious anemia has been called "pernicious anemia of pregnancy" It differs from the former however in several respects It is more commonly seen in women below the age of forty years free hydrochloric acid is present in about one half of the cases neurological manifestations are absent and recovery may follow transfusions or the termination of pregnancy It differs strikingly also as will be discussed later *in that it responds little if at all to*

parenteral injections of vitamin B_{12} but does react favorably to folic acid orally Furthermore the condition may not appear during the course of subsequent pregnancies One should differentiate these cases from those of a patient with true pernicious anemia who becomes pregnant as has happened in a number of patients under my observation

Recent studies have indicated that the macrocytic anemia of pregnancy may vary in different parts of the world Furthermore it is clear that our knowledge concerning this subject is incomplete and our present conclusions especially pertaining to the etiology must await the accumulation of additional information

At present a tentative classification of the macrocytic anemias of pregnancy and the puerperium may be made as follows

1 True addisonian macrocytic anemia in association with pregnancy
2 A mild macrocytic anemia probably due to a deficient intake of protein
3 The more severe type of macrocytic anemia which is resistant to standard doses of vitamin B_{12} and probably to even larger amounts
4 The macrocytic anemia seen in India which requires about four times the standard parenteral dose of vitamin B_{12} to produce beneficial results

TABLE VIII

THE RELATIONSHIP OF MACROCYTIC ANEMIA TO THE INTAKE OF ANIMAL PROTEIN AND THE VITAMIN B COMPLEX DURING PREGNANCY

Diet	*Incidence of Macrocytic Anemia (Per Cent)*
Daily Intake of Animal Protein Above 50 Grams	00 0
Daily Intake of Animal Protein Between 30–50 Grams	27 3
Daily Intake of Animal Protein Below 30 Grams	40 [illegible]
Daily Intake of Vitamin B (Thiamin)—Adequate	7 9
Daily Intake of Vitamin B (Thiamin)—Inadequate	28 9
Daily Intake of Vitamin B_2 Complex—Adequate	9 4
Daily Intake of Vitamin B_2 Complex—Inadequate	29 3

TABLE VIII —The above table shows observations on the food intake of 158 pregnant women with respect to the animal protein and vitamin B content of the diet. Our observations seem to indicate that there is a closer relationship between the intake of animal protein and the incidence of a macrocytic anemia than between such an anemia and a deficiency of either thiamine riboflavin or nicotinic acid
(Bethell Gardiner and MacKinnon Courtesy *Annals of Internal Medicine*)

Macrocytic Anemia Associated with a Dietary Deficiency of Protein — It has been found by Bethell and Blecha (38) that a mild macrocytic anemia occurs not uncommonly during the course of pregnancy and that this may be associated with an animal protein dietary intake of less than 50 grams daily In their patients in whom such an intake was 30 to 49 grams daily it was present in 10 per cent of the patients and in almost 14 per cent of those with an intake of 30 grams daily or less That

TABLE IX

MACROCYTIC ANEMIA OF PREGNANCY

	Average R B C (Per Cu Mm)	*Av Hb (Per Cent)*	*Av C I*	*Av M C V*
Lowest Change Due to Hydremia	3.53	67		
3 Months	3.70	67	0.98	95.9
4 Months	3.60	66	0.99	95.3
5 Months	3.48	66	1.03	101.1
6 Months	*3.43*	*63*	*1.03*	*101.7*
7 Months	3.71	67	1.00	97.8
8 Months	3.71	69	1.00	96.2
9 Months	3.88	71	0.98	94.2

TABLE IX—Changes in the blood characteristic of a mild macrocytic anemia of pregnancy. The lowest red blood cell count was 3.43 millions per cubic millimeter and at this same time the hemoglobin was 63 per cent. These changes must be regarded as indicative of an abnormal anemia of pregnancy because the red blood cell count and the hemoglobin are lower than the values observed in the physiological anemia of pregnancy and also because the cells are larger than normal size as indicated by a mean corpuscular volume of 101.7 cubic microns and the color index is greater than 1.00. This type of anemia of pregnancy responds favorably to folic acid therapy or a high protein diet.

protein may be concerned in some way with the cause of this anemia is suggested by the report of Coldhamer and his collaborators (41) who found that the addition of protein to the diet of a person with an extreme macrocytic anemia of pregnancy could cause the blood to re

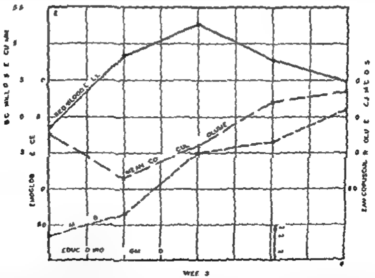

Fig. 8—The changes in the blood of a patient with the microcytic anemia of pregnancy are shown following the administration of iron. The initial blood examination showed a red blood cell count of 3.8 millions per cubic millimeter, the hemoglobin was 48 per cent, and the mean corpuscular volume 76 cubic microns. Following six weeks of iron therapy the red blood cell count had increased to 4.5 millions per cubic millimeter, the hemoglobin to 82 per cent, and the cell size to 87 cubic microns. In the two weeks postpartum period the values continued to increase. The findings in this case illustrate the gratifying results which may be attained in this type of anemia by the use of adequate doses of iron. (Bethell, courtesy *Journal American Medical Association*.)

turn to normal without additional therapy. Bethell (*13*) has also shown that this type of anemia is amenable to the administration of a minimum amount of 85 grams of protein of which at least 50 grams is in the animal form. From these observations it is clear that a protein deficiency is related to the macrocytic anemia of pregnancy but just how this exerts its effect is a matter still under consideration. There is of course the likelihood that the protein lack means a deficiency of the extrinsic factor which is readily supplied by the addition of milk, eggs and meat to the diet. This could explain the prompt and beneficial results of such therapy. That either the extrinsic or intrinsic factor is diminished is suggested strongly by the fact that the intramuscular injection of liver is specific for this type of anemia. No one has proven that there is a deficiency of the intrinsic factor in such patients. If this were true it

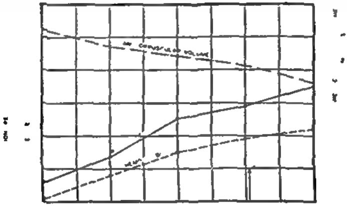

Fig. 9.—This chart shows the beneficial results which follow the administration of a high protein diet to a patient with the macrocytic anemia of pregnancy. At the beginning of the period on observation six weeks before delivery at term the red blood cell count was 3.[illegible] million per cubic millimeter, the hemoglobin 61 per cent, and the mean corpuscular volume 102 cubic microns. This patient was given protein which contained a minimum of animal protein of 50 grams represented by one quart of milk, one fourth pound of lean meat, and one egg daily. Note the increase in blood values to those considered to be normal for a pregnant woman at term. A more severe anemia due to this cause has for years been classified under the term of "the pernicious *anemia of pregnancy*." An anemia such as this will also respond to folic acid therapy but not to vitamin B_{12}. (Bethell, courtesy *Journal of American Medical Association*.)

must be transient because the patient may recover and never thereafter suffer from the condition. The possibility has been suggested (*13*) that a low protein diet may cause a fatty change in the liver, and hence prevent this organ from performing its function of storage of the antipernicious anemia factor and thus cause a macrocytic anemia.

Although Thompson and Ungley (*42*) state that a dietary deficiency was of possible significance in only 11 of their 27 patients, a scrutiny of their patients' dietary histories indicates that this is an understatement

The information which they give indicates that in only 3 of 27 patients was the diet satisfactory and in the remaining 20 patients it was either very poor or the intake of food was seriously impaired by loss of appetite or persistent vomiting The diets appeared to be deficient in meat eggs and milk in many instances or in other words in animal protein They consider however that such a diet could not be of significance from an etiologic standpoint only if it clearly preceded the onset of the anemia, which was the case in only 11 of the 27 patients This statement in my opinion, should be accepted with some caution It might be of importance if a woman had been ingesting an inadequate diet for a long time which was sufficient for all the needs of a non pregnant condition with the development of the gravid state however and an increase in the dietary requirements a relative deficiency might be created

Macrocytic Anemias Refractory to Vitamin B_{12} Therapy—In 1948 and also in 1950 Bethell and his associates reported (*43, 44*) that the administration of vitamin B_{12} in doses of 1 microgram daily failed to produce improvement in a patient with a severe anemia which developed in association with pregnancy This has been confirmed by a number of observers including Day and his associates (*45*) and Thompson and Ungley who have made a most comprehensive recent study of this subject (*42*)

The latter found that in general such anemias as observed in England did not respond to parenteral vitamin B_{12} injections when given in amounts that are known to be effective in patients with Addisonian pernicious anemia Furthermore they observed that refined liver extract was ineffective whereas the crude extract produced some response in about one half of the cases Folic acid was potent as was raw liver pulp which might have contained a sufficient quantity of folic acid to produce an effect Yeast extract accounted for a satisfactory result in about three fourths of the patients

One of the most extensive studies on the megaloblastic anemia of pregnancy and the puerperium which did not respond to vitamin B_{12} and included many severe cases is the one published by Thompson and Ungley (*42*) In their group of 45 cases the *tongue* was noted as being sore in 18 patients atrophy of the papillae was generalized in nine patients marginal in seven absent in 15 and was not recorded in 15 The tongue was clean in 20 patients furred in six and the condition was not recorded in 20 *Vomiting* occurred in the last months of pregnancy in 27 patients and in 14 of these it was severe persisting for four months or more The *spleen* was palpable in five of 38 patients and the *liver* enlarged in four patients all of whom had congestive heart failure Thirty five patients were specially examined for *neurological complications* but none were found Furthermore no patient in this group de

veloped changes in the nervous system following folic acid therapy and the authors state (42) that there are no such cases recorded in the literature

Gastric analysis following the injection of histamine was done in 41 cases free acid was present in 32 and absent in nine In one patient who initially had an achlorhydria free acid returned

The fact that vitamin B_{12} in adequate doses given parenterally does not produce a satisfactory response in this type of anemia indicates clearly that the condition is not due to a deficiency of the extrinsic factor or intrinsic factor of Castle or to a failure of absorption from the gastro intestinal tract As such patients respond promptly to folic acid orally one might infer that the condition results from a deficiency of this material This is difficult to reconcile with the knowledge that folic acid has a widespread distribution in many types of food The possibility arises however that its natural inactive conjugated form cannot be utilized normally by patients with such an anemia

The possibility that an increased destruction of erythrocytes may play a role in the etiology is considered by Thompson and Ungley (42) They cite the report of Lescher (46) and that of Callender (47) in support of this view The latter report is of special interest as one patient showed a red blood cell fall of 3 per cent a day which could only be accounted for by an increased destruction of erythrocytes Further more by a study of the survival of transfused red blood cells using the Ashby technic (48) it was found that the average life span of these red blood cells was only 25 9 days as compared to 50 days in a control group of patients with hypochromic anemia

The association of this anemia with pregnancy and the puerperium suggests that some hormonal disturbance may be concerned with the etiology of this anemia and there is some evidence which might support this For example it has been shown that there is an abnormal pattern of urinary hormone excretion in this condition (45) Thompson and Ungley (42) are of the opinion that possibly some abnormal steroid exists in pregnancy which is antagonistic to folic acid

Blood Changes in the Macrocytic Anemia of Pregnancy—*In most* instances the red blood cell count is in the vicinity of 3 0 to 3 5 millions per cubic millimeter and the hemoglobin from 9 8 to 10 9 grams per 100 cc of blood (60 to 70 per cent) The color index is 1 0 or slightly below There is usually a slight degree of macrocytosis as indicated by a mean corpuscular volume which is usually from 100 to 110 cubic microns

In the most severe cases the red blood cell count may be in the vicinity of 1 million per cubic millimeter the hemoglobin from 20 to 30 per cent and pronounced anisocytosis and poikilocytosis may be present The white blood cells are normal or reduced in numbers as in pernicious

anemia One such patient I saw just after my graduation from medical school had a count of approximately 1 million red blood cells per cubic millimeter and striking changes in the size and shape of the cells She was two weeks postpartum and seemed to be in extremis In my ignorance I communicated the information to the local physician that she had true pernicious anemia and would undoubtedly die He insisted however very correctly that there was a form of pernicious anemia associated with pregnancy from which patients recovered This fortunately occurred in the patient under consideration and she subsequently underwent a further pregnancy without a recurrence of the anemia

The important blood changes in the series of 45 cases studied by Thompson and Ungley (42) which included many with a severe anemia were as follows in 33 of the 46 patients the *initial red blood cell count* was 1 49 millions per cubic millimeter or less in 21 of these it was below 1 0 millions per cubic millimeter The *mean corpuscular volume* was 90 cubic microns or greater in 28 of 38 cases and in 12 of these it was between 110 and 140 cubic microns The *mean corpuscular hemoglobin* concentration was below 25 per cent in five patients from 25 to 29 per cent in 14 patients and greater than 30 per cent in 19 per cent The *mean corpuscular hemoglobin* was between 25 and 29 micrograms in 23 patients and between 30 and 35 micromicrograms in 16 patients The *white blood cell count* was less than 6000 per cubic millimeter in 24 patients In only seven of 43 patients was it greater than 10 000 per cubic millimeter *In summary it may be said that patients with the severe form of megaloblastic anemia of pregnancy* and the puerperium are most likely to have a red blood cell count below 1 5 million per cubic millimeter a white blood cell count between 6000 and 10 000 per cubic millimeter a mean corpuscular volume between 100 and 110 cubic microns and a mean corpuscular hemoglobin concentration greater than 30 per cent and a mean corpuscular hemoglobin between 25 and 29 micromicrograms

TREATMENT OF THE ANEMIAS OF PREGNANCY

As these anemias are so prevalent it would appear logical to employ effective *preventive measures* in all pregnant women to maintain the blood at normal level throughout the period of gestation This may be accomplished by very simple therapeutic measures *One is the addition* of iron in the form of ferrous sulphate 0 3 gram in enteric coated capsuls three times daily before meals If gastro intestinal symptoms result from the medication which occurs rarely in my experience then the iron medication can be given following meals If it still persists then ferrous gluconate 0 3 gram may be given before or after meals If complaints are still present then the dose should be reduced to the tolerance of the patient which may be one or two tablets daily This

should be done as soon as it is recognized that the state of pregnancy exists and continued until several weeks after delivery and throughout the period of lactation if the mother nurses the child Likewise attention should be given to the diet and provision made to be sure that at least 50 grams of animal protein are consumed daily This may be accomplished by having the pregnant women take a minimum of one quart of milk one fourth pound of lean meat and one egg daily By such simple means therefore it is possible that both the microcytic and macrocytic anemias of pregnancy can be averted in practically every case

The importance of the value of these measures cannot be overestimated It often permits lactation which otherwise would not be possible convalescence is expedited puerperal infection is less likely

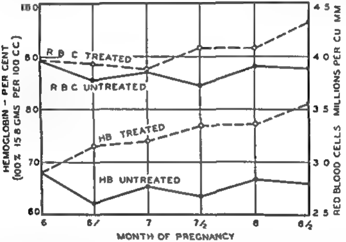

Fig 10 —A comparison between the levels of the hemoglobin and red blood cell count in normal pregnant women who received iron and those who did not in the last two and one half months of pregnancy It will be noted that the hemoglobin readings of both groups was 68 per cent at the beginning of the period of observation The red blood cell counts of the two groups averaged 3 9 per cubic millimeter In those receiving therapeutic doses of iron the hemoglobin at the end of two and one half months averaged 81 per cent whereas in the group who did not receive this medication the average hemoglobin reading was 66 per cent The effect of iron is also indicated by the difference in the levels of the red blood cell counts In the treated group the average count was 4 3 per cubic millimeter and in the untreated group it was 3 9 per cubic millimeter (Bethell courtesy *New York State Journal of Medicine*)

and perhaps most important of all it makes certain that the child will be born with adequate iron reserves If this were not done the hemoglobin and red blood cells would be normal at birth but the infant might develop an iron deficiency anemia during the first year of life The *treatment of hypochromic anemia* which has already developed during pregnancy differs very little from the prophylactic measures just discussed If the anemia is hypochromic then ferrous sulphate in the usual dose (0 3 gram 5 grains t i d a c) should be prescribed Within 10 days

to two weeks it should be doubled if there is not a satisfactory response It is better to administer this in enteric coated pills to avert gastro intestinal irritation although in my experience this has not been trouble some If there is a reduction in the red blood cell count below 3 5 millions per cubic millimeter then it is wise to be assured that the diet contains at least 50 grams of animal protein daily, as used in the prophylactic treat ment If the anemia is severe these amounts should be increased 50 per cent as also they should be in lactation If the iron medication is poorly

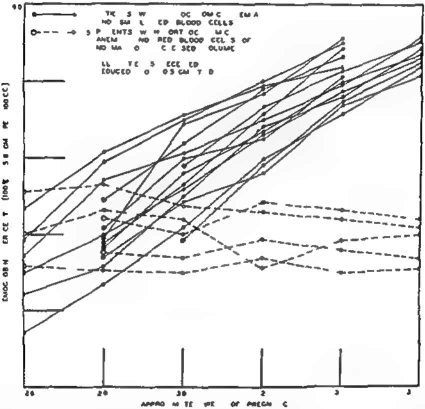

Fig 11 —The effect of administering iron to pregnant women with a hypochromic microcytic anemia as contrasted to the absence of any effect of this therapeutic agent on the macrocytic anemia of pregnancy The lines rising upward in each case of hypochromic microcytic anemia indicate a striking increase in the hemoglobin of the circulating blood whereas the horizontal line in each case of anemia of pregnancy associated with a normal color index and normal or increased cell size indicates that iron has no therapeutic effect in patients with this type of anemia (Bethell courtesy *Journal of the American Medical Association*)

tolerated then as stated above tablets of ferrous gluconate 0 3 may be given three times daily before or after meals if there is gastric irritation If all oral medication fails iron may be administered intravenously in the form of saccharated oxide of iron which is prepared in ampules containing 100 milligrams in 5 cc of fluid (For the method of administration and dosage reference should be made to page 96)

It is the opinion of Talso and Dieckmann (49) that the microcytic hypochromic anemia observed in pregnancy is not due simply to iron deficiency. They believe that in addition some other factor is lacking or that the defect lies in the mechanism of post absorptive iron utilization. Furthermore it is their opinion, with which I do not concur nor do the great majority of those who have been interested in the subject, that in the anemia of pregnancy "controlled observations indicate that the administration of these substances (iron alone and in combination with accessory factors) does not increase the rate of hemoglobin formation significantly."

It is of interest however that Dieckmann and his associates (50) report that the administration of molybdenum iron complex in a prophylac

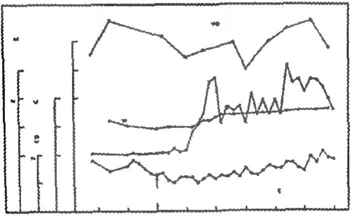

Fig 12.—Response of the reticulocytes to 96 grams of yeast daily in a patient with the pernicious anemia of pregnancy. In this patient after 96 grams of yeast had been added to her diet there was an increase in her reticulocytes to a peak of 30 per cent on the ninth day of administration. The elevation of the reticulocyte curve remained for a considerable period of time. As yeast contains about 50 per cent protein the favorable result was interpreted as due to the added protein to the diet. With the administration of protein in the form of milk, meat and eggs and omitting the yeast the red blood cell count and hemoglobin percentage rose to normal at term. Other factors as folic acid may have contributed to the favorable effect.

tic dose of three tablets" which they consider to be one half of the therapeutic dose caused a much higher hemoglobin concentration at term than in the control patients. It is difficult to understand why molybdenum iron should be superior to ferrous sulphate in appropriate doses, which has been an entirely satisfactory therapeutic agent in the treatment of iron deficiency anemia over many years. The Mol Iron tablets which are used in this series of patients each contained ferrous sulphate 195 milligrams and molybdenum oxide 3 milligrams. Three tablets daily, one half of the recommended dose, contains 120 milligrams of elemental iron.

Let me reiterate it is my opinion and that of many others who are familiar with this field that ferrous sulphate in doses of 0 3 to 0 6 gram t i d will control all cases of iron deficiency anemia of pregnancy If the anticipated response is not obtained then I would suspect (1) that the patient was not taking the medication as directed or (2) that the diagnosis was incorrect or (3) that chronic hemorrhage or an infection was present In such an event I would give intravenous iron in the form of saccharated oxide of iron

The *treatment of the macrocytic anemias of pregnancy and the puerperium* is highly satisfactory If a severe anemia is present a blood transfusion should be given immediately and repeated as long as indications are present *The most effective therapy is to administer 10 to 20 milligrams of folic acid orally a day which should produce a prompt response The action of vitamin B_{12} and liver extracts is nil or too uncertain to warrant their use* If hypochromia develops then iron in the form of ferrous sulphate 0 3 gram orally should be given before meals It is advisable to correct the patient's diet if it is abnormal and to insure in addition to a general balancing of the dietary intake that meat eggs and milk are eaten each day

The outlook in patients with the severe macrocytic anemia of pregnancy is good if properly treated Before specific therapy was available if blood transfusions could sustain the patient through pregnancy and the puerperium she usually recovered and in some instances went through another pregnancy without difficulty Before blood transfusions were available however the prognosis was ominous

It is reported by Thompson and Ungley (42) that in their group of 45 patients, many of whom had a severe macrocytic anemia there were no deaths Furthermore despite the fact that most of the patients stopped the treatment soon after leaving the hospital the relapse rate was low In 26 of the cases followed for periods of one to 14 years there was only one relapse and this occurred in a second pregnancy

The observations of Thompson and Ungley (42) also indicate that the outlook for delivery of a normal child is excellent In 46 pregnancies there were 47 live births including four twin pregnancies There were three stillbirths and two infants died shortly after birth

The Co existence of Various Blood Diseases with Pregnancy —It sometimes occurs that patients with various types of blood diseases become pregnant and the situation is then one in which the patient has two wholly unrelated conditions from the standpoint of etiology Both might have an important influence however on each other I have observed patients with pernicious anemia and with leukemia become pregnant and be delivered of a healthy child at term In the case of patients with pernicious anemia regular treatment with intramuscular liver extract 1 cc or 15 micrograms of vitamin B_{12} at least at weekly intervals and the

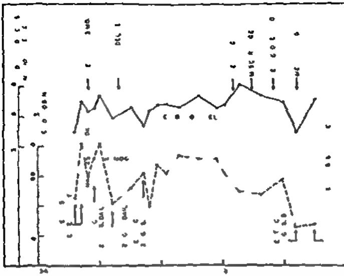

Fig 13 —Patient with pernicious anemia who went through a normal delivery at term without difficulty Throughout the pregnancy she received antipernicious anemia medication in the form of liver extract or ventriculin Two years later she again became pregnant but a miscarriage occurred at 3 months This was followed by a pelvic operation and later menorrhagia The latter resulted in the development of an iron deficiency which made necessary the addition of iron to the antipernicious anemia medication Experience has shown that since the introduction of effective antipernicious anemia medication a patient with pernicious anemia can bear children and pass through pregnancy in a normal manner provided the proper antipernicious anemia therapy is administered

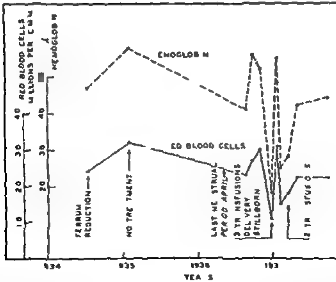

Fig 14 —Nineteen year old Negress with sickle cell anemia in whom the pregnancy terminated with the delivery of a still born infant The patient was carried through pregnancy without difficulty but given a number of blood transfusions at the time of delivery and shortly thereafter on account of the severe anemia which developed

Let me reiterate it is my opinion and that of many others who are familiar with this field that ferrous sulphate in doses of 0 3 to 0 6 gram t i d will control all cases of iron deficiency anemia of pregnancy If the anticipated response is not obtained then I would suspect (1) that the patient was not taking the medication as directed or (2) that the diagnosis was incorrect or (3) that chronic hemorrhage or an infection was present In such an event I would give intravenous iron in the form of saccharated oxide of iron

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tions have yielded living offspring Patients with sickle cell disease are particularly susceptible to infections and the complications of pregnancy and the clinical course is closely correlated with these associated disorders They recommend that such patients should be hospitalized early in pregnancy and be given optimum obstetrical care It is advised that repeated blood transfusions be given such patients for the anemia severe infections or impending shock They do not consider that the disorder per se is an indication for the interruption of pregnancy but if complicated by associated disorders abortion should be considered Pregnancy does not favor a remission of the disease and patients usually do not survive long enough to rear their children which in their opinion should be taken into account when sterilization is under consideration

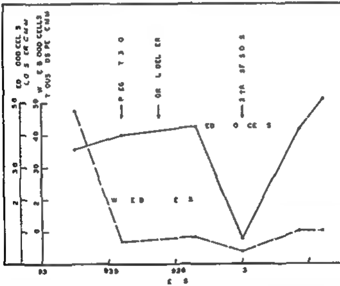

Fig 16 —A 38 year old woman who was first seen in 1934 by a surgeon for a scar over the right eye At this time the white blood cell count was 47 800 per cubic millimeter of which 79 5 per cent were in her lymphocytes or cells characteristic of lymphosarcoma She was delivered of a normal child in September 1935 and had no complaints or treatment during the pregnancy Death occurred in June 1939 as a result of the leukemia which had then been classified as definitely of the lymphosarcoma type The entire illness from the first appearance of enlarged glands in the neck and axillae which was 18 months before the patient was first seen by us until her death in 1939 was 5 years It is of interest to note that the patient s condition actually improved during pregnancy despite the lack of any form of treatment and the child was normal in all respects

The gravity of pregnancy in sickle cell anemia is emphasized by Fouche and Switzer (56) who state that the outlook for the mother and the child is ominous They consider that toxemia of pregnancy premature labor morbidity and mortality are definitely increased in these patients The treatment they recommend for the latent phase should be prophylactic

addition of at least one quart of milk two eggs, and one fourth pound of lean meat daily is indicated Certainly there is no reason to terminate a pregnancy in a patient with pernicious anemia, for with the modern treatment of the disease there is every prospect that the mother may have a normal blood throughout pregnancy and that the child will be healthy when born, as far as any type of blood dyscrasia is concerned

Among other hematologic disorders associated with pregnancy, the following have been reported (*51*) purpura (*52 53*), *sickle cell anemia* (54 55 56 57), *leukemia* (58) *aplastic anemia* (59 60 60a), *polycythemia* (*61*) and *pernicious anemia* (*61*a)

Pregnancy and Sickle Cell Disease—A comprehensive review of this subject with a bibliography of 76 articles has been written by Beacham and Beacham (*55*) In addition they have analyzed their experience

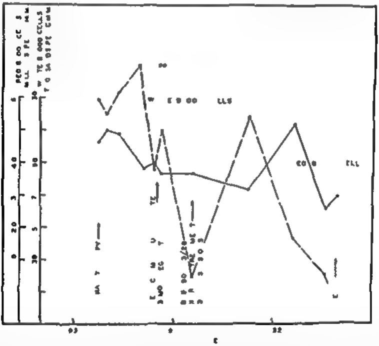

Fig 15—Patient with chronic myelogenous leukemia who was observed during pregnancy and following the delivery of a normal healthy child During the pregnancy the only treatment administered was ferric ammonium citrate to control the mild iron deficiency anemia of pregnancy which developed Roentgen ray treatment was withheld in order to avert possible injury to the fetus Immediately following the pregnancy roentgen ray therapy and blood transfusions were given with a satisfactory temporary response Death followed about 16 months after the child was born and almost three years after the patient came under our observation

with this complication of pregnancy of the Charity Hospital New Orleans Louisiana The incidence of sicklemia or the sickle cell trait in Negro obstetrical patients in New Orleans is about 6 per 100 000 deliveries About one in five mothers with sickle cell disease expires while classified as an obstetrical patient, and only approximately two thirds of the gesta

placenta acts as a barrier which prevents the maternal organism from transmitting the disease to the child in utero and also prevents the child with congenital leukemia from transferring the condition to the mother

Erf (58) concludes (1) that the course of leukemia is not altered by pregnancy (2) in acute leukemia abortion is not indicated on account of the acute course of the leukemic process and in chronic leukemia interruption of pregnancy is not advisable on account of the high percentage of normal offspring born at term (3) there is no consistent evidence that pregnancy increases the activity of leukemia lymphosarcoma or Hodgkins disease (one patient whom I observed with lymphosarcoma had a long remission during and following pregnancy with no other treatment than an occasional blood transfusion) and (4) the evidence indicates that x ray directed toward the pelvis may do injury to the fetus whereas if it is applied to other areas it "probably" would do no harm Radiophosphorus because it emits beta rays which travel only a few millimeters is probably less injurious to the fetus than roentgen irradiation (63) *It is my opinion however that the possible risk of injury following any form of irradiation applied as therapy during pregnancy is considerable and if employed great caution should be used* Certainly if directed toward the pelvis it is harmful and is contraindicated Dependence should be placed on blood transfusion antibiotics if infection is present, and possibly arsenic in the form of Fowlers solution which is recommended by Erf (63) Urethane nitrogen mustard and folic acid antagonists have not been used in a sufficient number of cases to permit a conclusion

It is the belief of Li McBride and Mettier (64) that pregnancy does not influence the prognosis in chronic myeloid leukemia They recommend that the disease be treated during pregnancy with Fowlers solution and irradiation over the long bones the spleen and the mediastinum In their opinion roentgen therapy thus employed can be used without injury to the fetus

Murphy and Johnson (65) comment on the rarity of the association of pregnancy with leukemia and suggest that this may be because females with the disease are frequently sterile This they attribute to secondary amenorrhea and massive leukemic infiltration of the genital tract They believe that leukemia has a definite effect on pregnancy as it predisposes to prematurity and to a high fetal mortality It is their opinion that pregnancy complicated by leukemia should be carried as near to term as possible Then delivery should be attempted in the usual manner Immediate cesarean section is indicated at any time if the mother fails rapidly provided the fetus is viable Successful antemortum delivery by cesarean section of a normal baby has been reported more than once (58 66) Postmortem sections are usually unsuccessful as death of the fetus commonly precedes that of the mother (67 68)

digitalization and induction of labor as soon as viability of the fetus is established. Furthermore, it is their opinion that women with known sickle cell disease should have therapeutic sterilization or adequate contraceptive measures.

Sudden death in patients with sickle cell anemia is discussed by Rigdon (57). He states that in the 24 cases of sickle cell anemia associated with pregnancy reported in the literature, sudden death has occurred in six of the cases. In his opinion, however, pregnancy is not a predisposing cause of sudden death as it also occurs in non-pregnant persons with the disease. He does take into account the possibility that the anemia which may be present in pregnancy makes more likely an anoxemia. It is his conclusion that vascular occlusions and hemorrhages within the brain secondary to the sickling of the erythrocytes are probably the most important factor in the cause of sudden death in this condition.

Leukemia in Pregnancy.—Pregnancy probably does not influence the course of leukemia importantly but the disease predisposes to premature delivery and a high fetal mortality. There is no instance of leukemia being transmitted to the fetus from the mother who is suffering from the disorder, and mothers who give birth to a child with congenital leukemia have no evidence of the disease. Roentgen ray therapy should be given with caution, if at all, to the pregnant woman with leukemia, and certainly the region of the pelvis should be avoided. Probably the only safe forms of therapy are repeated blood transfusions, antibiotic agents if infection is present, and possibly arsenic in the form of Fowler's solution.

In a study of 100 cases of leukemia complicated by pregnancy, Erf (58) has reached certain practical conclusions. In this collected group there were 87 cases of myeloid leukemia (24 acute and 3 chronic) and 13 cases of lymphatic leukemia (10 acute and three chronic). It is not surprising that acute leukemia carries with it an ominous prognosis in pregnancy as it does in uncomplicated cases. For example, of the 34 acute cases all died before or within three months after delivery. Furthermore, excluding abortions and maternal deaths before delivery, less than 50 per cent of the babies were normal when born of mothers with the acute form of the disease. In 66 cases of chronic leukemia, which was more commonly of the myeloid type, 43 survived more than one year after delivery and, excluding abortions and maternal deaths before delivery, 75 per cent of the babies were normal.

As previously stated, there have been no reports of a leukemic newborn being delivered of a leukemic mother, although there have been cases of leukemia in the newborn (congenital leukemia), but in each instance, however, the mother has been healthy (58). The placentas were normal in such cases. Pregnant leukemic mice are known to give birth to normal young (62). It is the opinion of Erf (58), in which I concur, that the

patients with malaria hookworm infestation septicemia either due to staphylococcus or the sterptococcus with chronic glomerulo tubular nephritis malignant disease and many other conditions It should be kept in mind that while the anemia may have a fortuitous association with pregnancy it may be accentuated by the chronic state in at least two ways (1) the pregnancy will place greater demands on the element which may be already deficient and responsible for the anemia such as iron or possibly vitamin B 12 or folic acid or (2) as a result of an increase in the total plasma volume due to physiologic reasons the level of the red blood cells and hemoglobin will be reduced by a dilution effect and therefore be lowered For example as stated elsewhere if the red blood cell count is 4 3 millions per cubic millimeter and the hemoglobin 12 6 grams the normal 26 per cent dilution occurring from the sixth to the ninth months will cause these levels to fall to 3 7 millions per cubic millimeter and 11 0 grams respectively

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Aplastic Anemia in Pregnancy.—A fatal case of idiopathic aplastic anemia ending in death during the fourteenth week of pregnancy has been reported by Hurwitt and Field (*60*). They reported the case of a 27 year old woman whose death resulted in the fourteenth week of pregnancy from an idiopathic aplastic anemia. These authors collected a total of 14 cases of aplastic anemia which occurred during the course of pregnancy. Of these only five survived. The uterus had been emptied by normal delivery in two and by interruption during the third trimester in two of the 14 cases. In one case the disease developed postpartum. They believe that the association of this variety of anemia with pregnancy is more than coincidental, in other words, that the gravidity may play an etiologic or conditioning role. It is their opinion that in the presence of such an anemia interruption of the pregnancy should be strongly considered.

More recently Maizels (*60*a) reports the case of an acute idiopathic aplastic anemia of pregnancy in a primigravida aged 28 years who recovered. The patient was treated with repeated blood transfusions and labor induced at the 36th week. The child was normal in all respects and the mother made a complete and rapid recovery.

Miscellaneous Blood Disorders Associated with Pregnancy.—The case of a 30 year old female with *polycythemia rubra vera* who became pregnant for the first time about one month after radiophosphorus was given is reported by Erf (*61*). She was delivered about eight months later of a five pound, eight ounce stillborn child, normally formed, but with a twisted cord. Four months later she became pregnant again, but no follow up is given concerning this pregnancy.

Pregnancy may occur in the course of *hemolytic anemia*. The same type of treatment should be given and for the same indications as in nonpregnant individuals. One patient about whom I was informed had hereditary sperocytosis (congenital hemolytic jaundice) with a moderately severe anemia and a spleen which extended a hand's breadth below the costal margin at the sixth month of pregnancy. Splenectomy was done with an excellent result, the anemia disappeared, and the pregnancy proceeded to term without incident and a healthy child was born. In the *acquired type or hemolytic anemia* complicated by pregnancy, cortisone should be given in the hope that a good result can be accomplished by this type of medication alone. If the blood fails to remain normal with this form of therapy, then an attempt should be made to bring it to normal again by treatment with cortisone and the spleen removed as early in pregnancy as possible. *Idiopathic thrombocytopenic purpura in pregnancy* may be a grave complication and deserves serious consideration when it occurs. It is discussed elsewhere (see page 650).

Various other conditions may be responsible for the anemia associated with pregnancy and may be accentuated by it. Anemia is observed in

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A classification offered by Estren and Dameshek (2) is as follows

I ANEMIAS ASSOCIATED WITH AN "INTRINSIC" ABNORMALITY OF THE RED BLOOD CELLS; HEREDITARY CONGENITAL HEMOLYTIC ANEMIAS

(1) With spherocytosis (congenital hemolytic anemia)
(2) With target and oval cells (Mediterranean syndromes)
(3) With target and sickle cells (sickle cell syndromes)
(4) Others

II ANEMIAS ASSOCIATED WITH FUNDAMENTALLY NORMAL BUT INJURED RED BLOOD CELLS

A *Injured by Extrinsic Agents*

1 Physical (burns Roentgen rays)
2 Bacterial (Bartonella)
3 Parasitic (malaria)
4 Allergic (fava bean)
5 Chemical (arsine phenylhydrazine sulfonamide lead)
6 Immunologic
 (a) Anti A anti B
 (b) Anti Rh
 (c) Certain acquired hemolytic anemias
 (d) Certain paroxysmal hemoglobinurias
 (e) Others?
7 Siderocytic
8 Toxic" (symptomatic)

B *Destroyed by Overactivity of Normal Hemolytic Mechanisms* *"Hypersplenic Hemolytic Anemia*

Classification of the hemolytic anemias as devised by Castle (3) follows

INCREASED BLOOD DESTRUCTION DUE TO

I EXTRINSIC CAUSES

Septicemias streptococcus Welch bacillus malaria bartonella
Chemicals lead arsine analine derivatives sulfonamides venoms
Heat thermal burns
Immunity natural transfusions of foreign cells or plasma
Immunity acquired Rh factor favism pollens

II INTRINSIC CAUSES

Abnormal erythrocytes congenital hemolytic jaundice sickle cell anemia paroxysmal nocturnal hemoglobinuria thalassemia
Abnormal plasma paroxysmal hemoglobinuria due to cold cold warm and acid activated agglutins hemolysins
Myelophthisic hemolytic anemia

CHAPTER V

THE HEMOLYTIC ANEMIAS

Definition.—A hemolytic anemia is one due to shortening of the life span of the erythrocytes associated with excessive destruction of red blood cells.

Normally, the red blood cells which are destroyed daily are replaced by an equal number. Consequently, the total erythrocyte count of the peripheral blood remains within normal limits. With an increase rate of blood destruction, unless there is an adequate compensatory increase in the number of red blood cells produced, an anemia of varying severity develops with the usual associated symptoms and signs. It should be kept in mind, however, that an increased rate of destruction of red blood cells does *not necessarily* result in an anemia, as the production may be augmented to the level where as many erythrocytes are formed daily as are destroyed, even at the accelerated rate.

Classification of the Hemolytic Anemias.—There is no classification of these anemias which is entirely acceptable to all who have made a study of the subject. This is chiefly because there still remains many controversial and unsettled points concerning the fundamental causes of the increased destruction of the erythrocytes in this type of anemia. The following is a classification offered by Haden (*1*).

I. Increased Hemolysis from Excessive Destruction of Cells Damaged by
   (1) Chemical agents (like phenylhydrazin)
   (2) Bacterial toxins (as in gas gangrene)
   (3) Iso hemolysins (as in incompatible blood groups) or immuno hemolysins (as in erythroblastosis)
   (4) Parasites (as in malaria)

II. Increased Hemolysis Due to Excessive Removal of Red Blood Cells Abnormal at Birth
   (1) Spherocytic anemia (familial hemolytic jaundice)
   (2) Sickle cell anemia
   (3) Oval cell anemia
   (4) Mediterranean anemia (*Cooley's anemia*)

III. Increased Hemolysis of Undetermined Cause (immune hemolysins, over activity of the spleen and other parts of the reticulo endothelial system, qualitative defect in stroma or hemoglobin, etc.)

type of hemolytic anemia For comparison a drawing of normal red blood cells is also given They state that the microcyte is perfectly spherical that its surface is entirely smooth and that its diameter is between 3 and 4 cubic microns Furthermore they noted that these cells do not form rouleaux but that they are constantly isolated and mobile Moreover they noted that distilled water changes the normal red blood cells to spherocytes With astonishing foresight they make the statement that "the jaundice of our patient appears to be a peculiar type of icterus The fact that the patient's mother and sister had a slight jaundice and that the sister had an enlarged spleen may indicate that this condition is one disease entity " Without the slightest question of a doubt it is apparent that this portrayal written 27 years before Hayem's observations in 1898 on acquired hemolytic anemia and 29 years before the descriptions of Minkowski establishes with a certainty a highly accurate and prior description which has until recent years apparently been overlooked

The case reported by Murchison in the second edition of his textbook published in 1877 (7) is of a male age 30 years who was "born yellow" and had been jaundiced as long as he could remember For three years before being observed he had suffered with gout The physical examination showed "decided yellowness of the skin and conjunctivae" The urine contained the bile pigments The liver was "slightly enlarged" It is of interest that this patient's brother who was about three years older also had been jaundiced all of his life and likewise suffered from gout The mother who died at the age of 54 for 14 years prior to her death had been incapacitated with gout and during this period she had been continuously jaundiced It is not of course possible to state that the three members of this family were suffering from chronic hemolytic icterus but this diagnosis is certainly a likely one There is no mention of splenomegaly and no information is available concerning the red blood cells In commenting on these cases Murchison states that this case is "remarkable not only for the persistence but for the hereditary character of the jaundice It must be admitted that the pathology of the jaundice in these cases is obscure It is clear that there is little or no obstruction of the bile duct "

The first accurate details of the clinical picture of chronic hemolytic anemia were given by Oscar Minkowski one of Naunyn's distinguished pupils before the German Society of Internal Medicine at its eighteenth meeting held in Weisbaden in April 1900 (8) He described the condition as an hereditary affection characterized by chronic jaundice urobilinuria splenomegaly and deposits of iron in the kidney In a study of the tissues of one of his patients who died of pneumonia he contributed the first pathological study of the disease to the literature His description was of importance because it showed that the liver was not the

The classification of the hemolytic anemias as employed by Whitby and Britton (4) is given below

A *Due to Infective Toxic, or Poisonous Factors*

1 *Infections* sepsis, streptococcal and staphlococcal septicemia Clostridium welchii infection malaria Oroya fever

2 *Poisons* Lead phenylhydrazine benzedrine sulfonamide drugs *phenothiazine sulphones* promin potassium chlorate novarsenobillon arseniuretted hydrogen dinitrobenzene naphthalene toluylene diamine and allied drugs phosphorus saponin ricin snake venom severe burns

3 *Allergy* Fabismus Baghdad Spring anemia

B *Due to Hemolysins*

1 Incompatible blood transfusion

2 Erythroblastic anemias of the neonatal period

3 Acute idiopathic hemolytic anemia (Lederer s anemia)

4 Subacute or chronic idiopathic hemolytic anemia

5 Symptomatic hemolytic anemia

6 Paroxysmal hemoglobinuria

7 Nocturnal hemoglobinuria

8 Experimental hemolytic anemia

C *Due Possibly to a Congenital Anomaly of the Erythron*

1 Congenital hemolytic icterus (acholuric jaundice)

2 Sickle cell anemia (African anemia)

3 Mediterranean anemia (target oval cell anemia, *Cooley s* anemia)

History —It has usually been stated that Murchison in 1877 was the first to recognize cases of hereditary hemolytic jaundice but recently Dreyfus (5) has directed attention to the remarkable publication of Vanlair and Masius (6) which appeared in 1871 six years before that of Murchison In this extraordinary contribution a great many of the essential details of this disorder including the changes in the blood are presented in accurate detail The authors recorded the case of a young woman who shortly after delivery became icteric and complained of recurrent attacks of pain in the splenic area The spleen was moderately enlarged and the stools highly pigmented It was said that her mother and sister had always been slightly jaundiced They emphasize that the main feature of the blood in this condition is the *sphericity* and the *small size of some of the erythrocytes* which differentiates them from normal red blood cells If there is any doubt concerning the accuracy of their description it is immediately dispelled when the colored plate accompanying their article is noted for here are shown the typical microspherocytes which are so highly characteristic of the hereditary

which may be so indolent that these point "possibly to some abnormal blood condition" Although Bettman (*12*) is said to be the first to mention the anemic blood picture and von Krannhals (*13*) four years later made similar observations it has not been previously emphasized that Vanlair and Masius in 1871 and Barlow and Shaw in 1902 made careful and detailed blood studies in their two patients with the disease In the son it was found by Barlow and Shaw that the red blood cell count fluctuated between 1 8 and 3 0 millions per cubic millimeter with a white blood cell count between normal and as high as 14 000 per cubic millimeter The hemoglobin estimation was between 38 and 50 per cent The mother was found to have an anemia of similar extent Leg ulcers are not common in this form of anemia but they do occur and are of interest but they are associated more commonly with sickle cell anemia They are known to be present in congenital hemolytic anemia however and are notorious for their resistance to all forms of therapy

Two of the special and highly significant characteristics of the blood in this condition were discovered by Chauffard namely the increased fragility of the red blood cells to hypotonic salt solutions and the fact that the reticulocytes or young red blood cells are increased in number in the circulating blood In 1907 Chauffard (*14*) discovered that the erythrocytes on one of his patients and two others on the wards of his colleague Widal were hemolyzed by hypotonic solutions of sodium chloride which had no effect on the red blood cells of normal individuals The diagnostic significance of such a change is great A few months later Chauffard and Fiessinger (15) described the presence on vital staining of a peculiar basophilic granulation of the red blood cells This material is now known as reticulum and is indicative of the fact that such cells are younger than those which do not possess it Chauffard s first studies were made by staining freshly prepared and fixed films of the blood with Pappenheim s solution (pyronin and methyl green) It is of interest to note that these granulations correspond closely with those described in the studies of Vaughan made in 1903 (*16*) W S Thayer and Morris refers to this (*17*) and make the rather caustic but *correct comment as follows "This subject is well discussed by Ferrata* who however in common with every continental author ignores Vaughan s excellent work" Vaughan who according to Thayer and Morris made the first careful studies on the vital staining of the red blood corpuscles found that these granulations were present in under 1 per cent of the red cells of normal individuals" It is known from subsequent observations that in persons with hemolytic jaundice the reticulocyte percentage is often over 10 and in some instances as high as 40 per cent or more

Hereditary hemolytic jaundice was first recognized in this country by Tileston and Griffin (*18*) who reported the condition as occurring in

cause of the jaundice and for the first time it was demonstrated that siderosis of the kidneys existed

In a second much more comprehensive paper, published in 1905 Minkowski (9) reported the case of two brothers who had been icteric since childhood with enlargement of the spleen and urobilinuria The father had succumbed to cirrhosis of the liver The grandmother four children and two grandchildren had presented the same anomaly since childhood In the opinion of Minkowski the entire clinical picture could be best explained on the basis of an unusual anomaly of the blood pigment metabolism possibly related to a primary change in the spleen This great clinician therefore ably described the important clinical features of the condition with the exception of those in the blood which he said showed no variation from normal

Claude Wilson (*10*) in 1890 gave a classical clinical description of a group of six consanguineous relatives in four generations who could hardly have had anything but congenital hemolytic jaundice although the blood studies were incomplete and noncontributory The disorder which he described was characterized by an enlarged spleen, accompanied by a sallow or subicteric complexion and appeared to be a hereditary condition The mother and two of her eldest children all with jaundice and enlarged spleens were seen by Sir William Gull the eminent clinician of his day who first described myxedema but in this instance he attributed the condition to malaria for which there was no convincing proof In addition some of these patients had attacks of chills fever and increasing jaundice which suggested strongly the crises of hemolytic jaundice In summing up the cases Wilson states that they are "known to be hereditary as they have descended from father to daughter and from mother to sons" He concludes his discussion of the etiology with the statement that "we seem to be thrown back upon regarding the condition as either a true hereditary malarial taint, or else as being something of a wholly different nature, of which we at present know nothing While confessing my inability to form any definite opinion upon these alternatives I may perhaps say the more I see and think of these cases the less do they remind me of malaria" In the way of treatment he mentions that in his opinion probably arsenic has been of value in raising the standard of health in some cases in others it appears to have had but little effect and in no case has it reduced the size of the spleen

Barlow and Shaw (*11*) described two cases in a mother and her son under the appropriate original title of "Inheritance of Recurrent Attacks of Jaundice and of Abdominal Crises with Hepato splenomegaly" This is a remarkably lucid and accurate clinical description noteworthy for at least two observations namely the presence of anemia in both patients and the original recognition that there may be leg ulcers in this disease

Determinations which give this figure are those of Shemin and Rittenberg (33, 34) with studies on isotropic protoporphyrin; observations on the persistence of sulfhemoglobinemia by Jope (35) and by blood transfusion of a different type into recipients and determining the interval which is required for the transfused red blood cells to disappear from the circulation (36, 37, 38, 39, 40, 41).

Apparently each group of red blood cells produced over a given interval *disintegrates in an orderly fashion as their life span of approximately* 120 days expires. Assuming such a period of the normal red blood cell to be 120 days, then about 0.83 per cent of the total number of erythrocytes would be destroyed daily. This represents the number present in about 50 cc. of blood.

The Formation of Bilirubin and Urobilinogen from Hemoglobin.—The synthesis of hemoglobin, a conjugated protein, is accomplished by the union of protoporphyrin with iron and globin, the latter constituting 96 per cent of the molecule and the iron 0.334 per cent. The process of the conversion of hemoglobin into bilirubin and finally urobilinogen, according to our present understanding, occurs as follows: in brief, after 120 days the red blood cells become effete, the hemoglobin is liberated and the initial chemical changes begin.

The first step of the disintegration of the molecule is the opening of the ring structure of protoporphyrin and the formation of a product, iron biliverdin globin (verdohemoglobin or hemosiderin). The iron is then removed by the reticulo-endothelial system and the product is then designated as bilirubinglobin, which gives the indirect van den Bergh test. The iron thus derived combines with serum albumin to circulate as serum iron. The iron free compound which remains is bilirubinglobin. With some limitations discussed later, the level of bilirubinglobin is an index of the rate of erythrocyte destruction. This substance having a large molecule does not escape from the blood stream through the kidneys and hence as in hereditary hemolytic jaundice bile is absent from the urine. Bilirubinglobin is excreted by the hepatic cells into the bile and becomes bilirubin separated from the globin molecule. As such it gives a direct van den Bergh reaction. The bilirubin which is excreted into the intestine is acted upon by the bacteria of the intestinal tract to become urobilinogen. This substance may undergo at least three other changes as follows: (1) it may be absorbed from the intestinal tract, carried to the liver by the blood stream, reconverted to bilirubin and excreted in the bile; (2) after reaching the blood stream it may be carried to the kidneys and excreted in the urine (normally this amounts to 1–2 milligrams per 24 hours); and (3) the bulk is excreted in the feces (50 to 200 milligrams per day). A diagram showing these changes appears on page 147.

Physiologic and Pathologic Methods of Destroying Red Blood Cells in the Body.—It is certain that normally the destruction *of red blood cells* proceeds at a given rate in the body and that approximately the number

four families A year later Thayer and Morris (17) gave a complete review of the literature up to that date and published their observations on two patients with the disease

Eppinger and Charnas in 1913 (19) were the first to call attention to the striking increase in fecal urobilinogen in cases of hemolytic jaundice The observation by van den Bergh in 1916 that the plasma bilirubin in the disease exhibits a delayed or indirect reaction (20) has been widely confirmed

Splenectomy as a form of therapy was first performed in patients with acquired hemolytic jaundice In 1907 Vaquez and Giroux reported on the initial attempt to remove the spleen in a patient with this type of anemia with a fatal result (21) A second patient with acquired hemolytic anemia in whom splenectomy was done had striking improvement as reported by Micheli in 1911 (22) Two similar cases were published by Banti (23 24) The favorable effect of the operation in a patient with hereditary hemolytic anemia was first reported by Kahn (25) The earliest general article dealing with the results of splenectomy was written by Eppinger and Ranzi in 1914 (26) By 1917 W J Mayo was able to report that in 19 cases in which this operation was done for hemolytic jaundice at the Mayo Clinic there was a fatality in one patient which gave a mortality rate of only 5 3 per cent

The acquired type of hemolytic jaundice was discussed by Widal Abrami and Brule in 1907 (27) although apparently Hayem (28) had recognized similar cases in 1898 for which he had proposed the name chronic infectious icterus of the paroxysmal variety with splenomegaly This type of anemia was investigated by the French school and studies on fragility reticulocytosis auto agglutination and hemolysins were made by Chauffard and his pupils especially between the years 1907 and 1909 and Widal and his associates during the same interval As pointed out by Dameshek and Schwartz (29) however with the advent of the World War in 1914 these investigations were abruptly terminated In 1925 the report of Lederer (30) dealing with acute hemolytic anemia was regarded as a new clinical entity but as Dameshek and Schwartz (29) say this was a rediscovery of a syndrome which had been lost sight of for more than a decade

As previously mentioned it was first noted by Vanlair and Masius (6) in 1871 that the typical cells in hemolytic anemia of the hereditary type were microspherocytes In 1907 Chauffard made the observation that the average diameter of the cells in this condition was less than normal It was Naegeli however who in 1919 first employed the term spherocyte (31) to such cells

The Life Span of the Erythrocyte—Until recent years the life span of the red blood cell was considered to be about 30 days (32) At present, however more accurate studies are in approximate agreement that the survival time under normal conditions averages about 120 days

Determinations which give this figure are those of Shemin and Rittenberg (33 34) with studies on isotropic protoporphyrin observations on the persistence of sulfhemoglobinemia by Jope (35) and by blood transfusion of a different type into recipients and determining the interval which is required for the transfused red blood cells to disappear from the circulation (36 37 38 39 40 41)

Apparently each group of red blood cells produced over a given interval disintegrates in an orderly fashion as their life span of approximately 120 days expires Assuming such a period of the normal red blood cell to be 120 days then about 0 83 per cent of the total number of erythrocytes would be destroyed daily This represents the number present in about 50 cc of blood

The Formation of Bilirubin and Urobilinogen from Hemoglobin —The synthesis of hemoglobin a conjugated protein is accomplished by the union of protoporphyrin with iron and globin the latter constituting 96 per cent of the molecule and the iron 0 334 per cent The process of the conversion of hemoglobin into bilirubin and finally urobilinogen according to our present understanding occurs as follows in brief after 120 days the red blood cells become effete the hemoglobin is liberated and the initial chemical changes begin

The first step of the disintegration of the molecule is the opening of the ring structure of protoporphyrin and the formation of a product iron biliverdin globin verdohemoglobin or hemosiderin The iron is then removed by the reticulo endothelial system and the product is then designated as bilirubinglobin which gives the indirect van den Bergh test The iron thus derived combines with serum albumin to circulate as serum iron The iron free compound which remains is bilirubinglobin With some limitations discussed later the level of bilirubinglobin is an index of the rate of erythrocyte destruction This substance having a large molecule does not escape from the blood stream through the kidneys and hence as in hereditary hemolytic jaundice bile is absent from the urine Bilirubinglobin is excreted by the hepatic cells into the bile and becomes bilirubin separated from the globin molecule As such it gives a direct van den Bergh reaction The bilirubin which is excreted into the intestine is acted upon by the bacteria of the intestinal tract to become urobilinogen This substance may undergo at least three other changes as follows (1) it may be absorbed from the intestinal tract carried to the liver by the blood stream reconverted to bilirubin and excreted in the bile (2) after reaching the blood stream it may be carried to the kidneys and excreted in the urine (normally this amounts to 1–2 milligrams per 24 hours) and (3) the bulk is excreted in the feces (50 to 200 milligrams per day) A diagram showing these changes appears on page 147

Physiologic and Pathologic Methods of Destroying Red Blood Cells in the Body —It is certain that normally the destruction of red blood cells proceeds at a given rate in the body and that approximately the number

which are destroyed are replaced each day The exact method of destruction under normal and pathological conditions however, is not known It is recognized at present that at least four possibilities must be considered It must be admitted, however, that our knowledge concerning this important mechanism is incomplete

The possible recognized methods of destruction of the red blood cells under normal as well as pathological conditions may be considered as follows (1) mechanical destruction (2) phagocytosis (3) hemolysis and (4) osmotic lysis

It has long been recognized that *mechanical destruction* is the most likely normal mode of destroying the red blood cells in the circulation As Rous points out in his classic review of the subject up to 1923 (*42*) this idea is not new for it was emphasized by Meltzer (*43*) in 1900 As Rous says nor will it seem strange to anyone who has watched in the living animal a red cell saddle bagged at a capillary fork pulled well nigh in two with its bagging portions continually belabored and dragged upon by its passing fellows It is known that mechanical fragility may be increased by various factors Miller and Dameshek (*44*) Stats (*45*) and Tasi and his associates (*46*) have demonstrated that agglutinated red blood cells have an increased mechanical fragility The studies of Shen Castle and Fleming (*47*) emphasize the importance of spheroidicity cohesion of red blood cells increased hematocrit and *changes in the strength of the erythrocyte membrane in relation to* greater osmotic and mechanical fragility I agree with Castle (*48*) that mechanical destruction is the most likely form of destruction normally and in many pathological conditions

Phagocytosis of the erythrocytes by reticuloendothelial cells may occur in certain pathological conditions Rous (*42*) considers it to be a factor in the normal mechanism of blood destruction It is doubtful however if such a mechanism is of primary importance in pathological conditions although it is observed at necropsy in the spleen and marrow in pernicious anemia and other blood dyscrasias

Hemolysis by specific agents in plasma undoubtedly causes lysis of the red blood cells in certain pathological conditions but it is improbable that it is a normal mechanism As early as 1908 Chauffard and Troisier (*49*) reported an immune hemolysin in the blood serum of a patient with acute hemolytic anemia Studies in recent years have demonstrated the importance of antibodies in incompatible blood transfusions in erythroblastosis fetalis in various types of paroxysmal hemoglobinurias and in some of the acquired hemolytic anemias

Osmotic Fragility —When normal red blood cells are placed in hypotonic saline solutions they undergo certain changes which eventually lead to rupture of the erythrocyte and discharge of the hemoglobin Studies by Ponder (*50*) indicate that when various substances are

employed to destroy the cell at least two types of hemolysis may occur

(A) Reduction of the surface area of the cells with hemolysis by saponin produces the following alterations in shape biconcave disk crenated disk crenated sphere smooth sphere and a prolytic sphere

(B) Lysis by hypotonic media is characterized by changes in both volume and shape as follows progressive increase in the swelling of a biconcave disk sphere progressive increase in volume of swollen sphere hemolysis

It has been emphasized by Castle and Ham (51) that stasis or as they say "erythrostasis may cause increased mechanical fragility and also osmotic lysis of erythrocytes Their conclusions are based on the observation that if red blood cells are incubated while suspended in serum or saline solution there is an increase in spheroidicity and osmotic fragility Some of the cells thus treated exhibit lysis They interpret these observations as suggesting that when blood is sequestered in the spleen or hemorrhagic infarcts there is a likelihood of hemolysis on account of increased mechanical osmotic fragility

From a clinical standpoint these changes are important because they indicate that as the erythrocyte assumes a spherical shape they are approaching the stage of hemolysis and disintegration Such a state is observed in patients with hereditary hemolytic jaundice in which many of the circulating red blood cells show a spheroidicity and hence are more fragile This can be demonstrated by placing them in varying dilutions of hypotonic saline solutions (see page 142)

An excellent summary of the present state of our knowledge concerning hemolysis is given by Estren and Dameshek (52) They state in part In final analysis hemolysis must be due to rupture of the envelope of the red cell Ultimate rupture of this envelope is believed to occur in the reticulo endothelial system of which the spleen comprises the greatest single unit" They consider that many factors combine to cause changes in the red blood cell envelope but the most important of these are (1) the constant buffeting of the red cell in its passage through the many miles of capillaries and (2) physical and perhaps chemical changes in the environment of the erythrocytes continually occurring during recurrent periods of stasis ("erythrostasis) in the spleen and other sinusoids is emphasized especially by Castle and Ham

According to Estren and Dameshek (52) it is possible to suggest three mechanisms for the production of hemolytic anemia from a theoretical standpoint

(1) The destruction by the reticuloendothelial system of intrinsically abnormal red blood cells as target cells sickle cells oval cells and spherocytes

(2) Injury to the red blood cells by a variety of agents such as antibodies in the blood plasma so that they become vulnerable and like

other injured erythrocytes are destroyed preferentially by the reticulo endothelial system

(3) Normal red blood cells are destroyed by an abnormal reticulo endothelial system in other words hyperactivity of the normal hemolytic forces may cause a hemolytic anemia in the presence of both normal erythrocytes and normal plasma

The Role of the Spleen —The exact role of the spleen in the etiology of the hemolytic anemias is unknown It is uniformly agreed that this organ is related importantly to the causation of these conditions but just how it contributes to their fundamental etiology remains an open question As splenectomy results in a cure in practically all cases of congenital hemolytic anemia and a considerable number of the acquired type it must be admitted that this organ is significantly concerned in the production of such types of anemia The fact that in congenital hemolytic anemia splenectomy results in a cure of the condition but the erythrocytes still remain spherical in shape and therefore have increased fragility suggests that although the spleen is the immediate cause of the anemia the hereditary spheroidal shape is the underlying cause

It is difficult to evaluate the importance of stagnation of blood in the spleen a state designated by Ham and Castle (*51 53*) as erythrostasis" and its relation to the hemolytic anemias It has been shown that when blood remains in the spleen the erythrocytes tend to become spheroidal thence more fragile and easily destroyed probably due to changes in osmosis and the pH

It has been found by Bergenhem and Fahraeus (*54*) that the normal blood contains a lytic substance to which they have given the name lysolecithin Furthermore these investigators have suggested that it becomes increased in amount in stasis and hence may be responsible for normal blood destruction in the spleen which is the chief organ of stasis in the body They suggest further that the hemolytic anemias might be due to an increased concentration of lysolecithin acting on the red blood cells as they pass slowly through the spleen This has been disputed by Singer (*55*) who concluded that although this substance has hemolytic qualities it is not the hemolysin causing hemolytic anemia

The Concept of Hypersplenism —Hypersplenism may be defined as a state characterized by abnormal functioning of the spleen in which either the red blood cells the granulocytes or the platelets or all of these elements may be destroyed in excessive numbers or their formation inhibited giving rise to hemolytic anemia primary splenic neutropenia or to thrombocytopenia or a pancytopenia Usually there is a pronounced selective action on one of these elements with minor effects on the other two The processes may arise as a primary condition from unknown causes or secondary to some recognized disease such as Felty s syndrome syphilis, Gaucher s disease sarcoidosis malaria Hodgkin s disease or

leukemia A concise review of the problem of hypersplenism is given by Kracke and Riser (56)

There are two main theories which serve to explain the concept of hypersplenism The first championed especially by Doan (57) considers that the spleen sequesters and then destroys the blood elements and the second sponsored chiefly by Dameshek and Estren (58) which assumes that in hypersplenism the organ elaborates a hormone which exaggerates the normal inhibiting mechanism of spleen on the formation of the blood elements and at the same time destroys effete red blood cells Doan concludes (59) that The concept of splenic hormones is intriguing but all evidence to date calls for acceptance with conservative skepticism albeit the maintenance of a continuing open mind" It is believed by Dameshek and Estren (58) that hypersplenism results from the inhibitory effects of the spleen on the bone marrow that phagocytosis if present involves the red blood cells chiefly that both mechanisms may be operative in some cases that delayed or partial response in some cases suggests that some other organ may also be concerned that regardless of the accuracy of the theory splenectomy is usually curative in patients with primary hypersplenism

Clinical Evidence of Excessive Hemolysis—Regardless of the underlying cause when excessive hemolysis of erythrocytes occurs there are certain manifestations apparent which are common to all hemolytic anemias When these are present therefore such an anemia should be suspected These may be discussed under the headings of changes in (1) the erythrocytes (2) the bone marrow (3) alterations in hemoglobin metabolism and (4) splenomegaly

Changes in the Blood—In the presence of increased hemolysis there is usually an *anemia* present This does not always occur however because red blood cell production in the bone marrow may proceed at such an augmented rate that it compensates for the excessive number of red blood cells destroyed In "crises" with striking blood destruction which may occur in all types of hemolytic anemia the red blood cells may be reduced to the vicinity of 1 0 million per cubic millimeter In many instances however in which hemolysis is not excessive the number of cells for long intervals especially in patients with congenital hemolytic anemia may be between 3 5 and 4 0 millions per cubic millimeter The erythrocytes are usually *normochromic* as the hemoglobin is not lost from the body Exceptions to this are observed in Mediterranean and sickle cell anemia as in these conditions there is an associated defect in hemoglobin metabolism

One finding in patients with hereditary hemolytic anemia and in most of those with the acquired types is the presence of small dense appearing *spherical cells* (spherocytes) in the peripheral blood When these cells are observed the diagnosis of hemolytic anemia is at once suggested

As they are thicker than normal being spherical, they are relatively fragile and consequently are *less resistant to hypotonic solutions* According to Watson (60) if the erythrocyte measurements and the morphology of the red blood cells in the stained smear clearly indicate a spheroidocytic anemia increased fragility is almost always demonstrable *Target cells* and *sickle cells* are thinner than normal and hence are more resistant to hypotonic solutions Also in patients with hemolytic anemias there is often an increased number of large cells which with vital stains can be shown to be young cells or *reticulocytes* In 90 per cent or more of all types of hemolytic disorders there is an increase in the percentage of reticulocytes usually averaging 10 to 20 per cent but in rare instances they may be 50 per cent or higher With Wright's stain there may be stippling of the red blood cells and frequently but not always *normoblasts in the circulating blood sometimes in large numbers*

The *bone marrow* in patients with hemolytic anemia is always hyperplastic indicating that a large number of cells are being released to the circulating blood It is of the normoblastic type Fifty percent or more of the cells in the marrow are usually found to be of the erythrocytic series instead of the normal number which is usually about 20 per cent Frequently many mitosis are observed

Hemoglobin destruction is accelerated in all patients with hemolytic anemia The only constant evidence of this observed in all patients is an *increased urobilinogen excretion* in the feces and usually in the urine It is true that usually in hemolytic anemia there is pallor with slight jaundice the latter being due to an increased bilirubin in the blood As this is bound bilirubin which does not pass through the kidneys there is no bilirubin in the urine and hence the jaundice is said to be *acholuric* The urobilinogen in the urine is usually greatly increased It should be noted however that an increased destruction of erythrocytes may be constantly present in the absence of an anemia jaundice or an increase in the urobilinogen of the urine This is because the bone marrow may compensate adequately by producing an increased number of red blood cells and the liver may be able to convert even the excessive amount of indirect bilirubin presented to it to direct bilirubin Hence there may be no jaundice as bilirubin does not accumulate in the blood Furthermore, the urine urobilinogen may not appreciably increase but the *excess fecal urobilinogen which is invariably present in hemolytic anemia* indicates an increased destruction of hemoglobin The point is made by Estren and Dameshek (61) that sometimes the only definite indication of excessive hemolysis is an increase in the fecal urobilinogen A hemolytic anemia therefore cannot be excluded unless a quantitative estimation for urobilinogen in the feces is done and found to be within normal limits

In almost all patients with hemolytic anemia the *spleen is moderately enlarged* There are however some important exceptions to this state

ment. In some patients, as those with Mediterranean anemia, the spleen may be huge, although this is uncommon. In other patients with a definite hemolytic anemia, as the sickle cell type, the spleen may be atrophic, although splenomegaly may be observed during the early stages of the disease. In general, however, in the hereditary type of hemolytic anemia and in many instances of the acquired type, there is a slight to moderate increase in the size of the spleen. By this is meant that the edge can be felt at the end of a deep inspiration or that it is palpable one to three finger breadths below the costal margin. It should be kept in mind, however, that the spleen may be 3 to 4 times as large as normal

TABLE X

METABOLISM OF HEMOGLOBIN

Protoporphyrin iron-globin	(Hemoglobin)
↓	Ring opened by reticuloendothelial system
Biliverdinglobin iron	(Hemosiderin)
↓	Iron removed by reticuloendothelial system
Bilirubinglobin	(Gives indirect van den Bergh)
↓	Globulin removed by hepatic cell
Bilirubin	(Gives direct van den Bergh)
↓	
Urobilinogen	(Stercobilinogen and Mesobilirubinogen)

↙	↘	↘
Absorbed, converted by liver to bilirubin and re-excreted in bile	Absorbed and excreted by kidneys (1–2 mg. per 24 hours)	Excreted in feces (50–200 mg. per 24 hours)

(After Estren, S., and Dameshek, W.: *Advances in Clinical Medicine*, Chicago, The Year Book Publishers, Inc., Vol. III, p. 49, 1949 (15).)

and still not be palpable. The splenic enlargement is due to its engorgement with damaged erythrocytes which are undergoing destruction by cells of the reticuloendothelial system present in greatest number in this organ.

Index of Hemolytic Destruction.—According to Miller, Singer and Dameshek (62), the output of urobilinogen in the urine and feces is a useful index of hemolytic destruction. After formation of urobilinogen from bilirubin in the intestines, it is thought to undergo one of three processes: (1) absorption from the intestine and conversion by the liver again into bilirubin and re-excretion into the bowel as bile pigment; (2) absorption from the intestine into the general circulation, where it is

excreted as urobilinogen in the urine in amount averaging 1 to 2 milligrams daily which gives a positive test in a dilution of 1–10 (3) chiefly by excretion into the feces in several oxidation forms which are included in the collective term of urobilin The amount of urobilinogen excreted in the feces normally fluctuates between 50 and 100 milligrams daily It may vary more extensively than this depending upon several factors as follows

(1) The amount excreted is influenced by the endogenous metabolism of urobilinogen and intestinal motility

(2) There are individual variations which are proportional to the total mass of circulating hemoglobin in the blood This latter value may be calculated from the concentration of hemoglobin per 100 cc of blood and the total blood volume

(3) As the sole source of fecal urobilinogen is thought to be the hemoglobin of the red blood cells which have undergone destruction it is possible to express mathematically the relationship between the excreted pigment and the total mass of circulating hemoglobin According to Miller Singer and Dameshek (62) this relationship or the 'hemolytic index as they call it should be a more reliable indicator of the degree and rapidity of hemolysis than the fecal content of urobilinogen alone Such an index is derived from the following equation

$$\text{Hemolytic Index} = \frac{\text{Average of 4 days daily output of fecal urobilinogen (mg)} \times 1000}{\text{Hemoglobin (gm per 100 cc)} \times \text{total blood volume/100}}$$

This index gives the amount of urobilinogen excreted in the stools daily from 100 grams of hemoglobin In employing this equation it has been found feasible to take the average daily output of urobilinogen for four days and to employ the expected blood volume as calculated from the formula of Gibson and Evans (63) The results obtained by this method of estimating hemolysis are as follows the normal hemolytic index was found to vary between 11 1 and 20 8 which indicates that at least a minimum of 11 1 mg of urobilinogen is normally derived from 100 grams of hemoglobin A decreased index was found in patients with polycythemia hypochromic anemia and in the post splenectomy state In these conditions the decrease varied between 20 and 69 per cent An increase was found in a number of conditions as follows pernicious anemia from 204 to 1131 per cent in congenital and acquired hemolytic anemia from 287 to 1672 per cent in Cooley s anemia from 700 to 2159 per cent and in one case of Gaucher s disease 61 per cent

There are various changes which are commonly associated with an increase in the hemolysis of red blood cells and therefore found frequently in patients with various types of hemolytic anemia None of

these are specific indicators however that the anemia is of the hemolytic type as they may be observed in other conditions not related to increased destruction of the red blood cells The alterations commonly associated with hemolytic anemias are jaundice of the acholuric type an indirect van den Bergh reaction for bilirubin in the circulating blood increase in urobilinogen in the urine a normochromic normocytic or macrocytic anemia leukocytosis and reticulocytosis. In the opinion of Miller and his collaborators (62) however the only constant indicator of increased hemolysis is an increase in the fecal content of urobilinogen

CONGENITAL HEMOLYTIC JAUNDICE

Synonyms —Hereditary spherocytosis familial spherocytosis chronic acholuric jaundice

Definition —A chronic hemolytic anemia with acute exacerbations characterized by a non obstructive jaundice without bilirubinuria with spherocytosis increased osmotic and mechanical fragility of the red blood cells reticulocytosis and an enlarged spleen The condition is hereditary and is transmitted as a mendelian dominant characteristic

Etiology —*Age* —The disorder has been recognized in some patients even at the age of a few weeks or a few months In some instances it is so mild that the clinical manifestations are not recognized until late adult life

Sex —Males and females are affected with equal frequency

Race —It is stated by Sherer and Cecil (64) that many textbooks describe congenital hemolytic anemia as occurring in all races and climates In their experience however after examining the blood of many Negroes in the past they have never encountered the disease in this race These authors observed a 14 year old dark skinned negro girl who undoubtedly had congenital hemolytic icterus In studying the family history it was found that in addition to the patient microspherocytosis occured in her grandmother on the mothers side and also in the uncle on the fathers side They conclude that it is possible to observe this type of anemia in full blood Negroes The possibility arises that the condition is seen only in negro families in which there has been inbreeding More recently McCormack and Simon (65) have reported a case in a negress and summarized the literature dealing with this topic

Heredity —It has been established definitely that the *disorder is a congenital one and is transmitted as a dominant mendelian trait by either parent* The most complete study has been that of Gansslen (66) who investigated 120 cases in southern Germany from the standpoint of hereditary transmission It has been possible to trace the condition through several generations A more recent study of the inheritance and linkage relations of acholuric jaundice has been made by Race (67) in

which he confirms the previous opinion that the disease is transmitted as a mendelian dominant trait

There may be *no history of a similar case in the family* but this may be because the condition in the parent was exceedingly mild and did not produce symptoms which were conspicuous enough to attract attention In one patient of mine a young girl with all the classical features of the disease the mother who accompanied her for the examination denied on direct questioning all family history of the disease It was noticed however that the mother was slightly jaundiced and further examination disclosed a definite splenomegaly moderate anemia and other evidences of the disease In addition she finally recalled that the maternal grand father of the patient had died many years ago in the University Hospital of the University of Michigan following a splenectomy Reference to his history of many years ago indicated that he also had suffered from this condition and splenectomy had been attempted in hope of a cure The mere statement therefore that another case does not exist in the family is not sufficient evidence to eliminate the condition and in all such instances an attempt should be made to examine the blood of both the mother and the father and other close consanguinous relations

According to Young *et al* (68) when evidence of hereditary sphero cytosis cannot be demonstrated in the relatives especially both parents one should suspect gene mutation low gene penetration illegitimacy or the confusion of hereditary spherocytosis with the acquired type

Pathogenesis —The following statements seem to be established in relation to the etiology of congenital hemolytic anemia

1 The red blood cells in this condition have an increased thickness or spherodicity which is inherited as a mendelian dominant characteristic this change in shape accounts for their increased fragility to hypotonic solutions and mechanical trauma

2 *The reticulo endothelial cells especially those in the spleen* remove these injured cells from the peripheral blood more rapidly than the hyperplastic marrow can produce them and consequently an anemia develops

3 The spleen is immediately responsible for the anemia but as the erythrocytes still remain abnormal in shape following splenectomy it is obvious that the underlying but wholly unknown fundamental cause of the anemia *the spherocytosis has not been affected* although all of the clinical manifestations disappear

There are three principal views concerning the etiology of this con dition The first originally stated by Naegeli (69) is concurred in by others including Gansslen (70) Haden (71) Thompson (72) Vaughan (73) Gripwall (74) Lloyd (75) and Loutit and Mollison (76) These observers consider that the cause is an inherited abnormality of the erythrocytes causing *them to assume a spherical shape* and therefore

rendering them more susceptible to injury. The second concept sponsored by Dameshek (77) suggests that the erythrocyte is normal when it leaves the bone marrow but that some extrinsic factor causes it to assume the spheroidal shape. The third view, that the anemia is due to hypersplenism, is supported chiefly by Doan and his associates.

The most generally accepted theory by far is the one originally proposed by Naegeli (69) and supported by numerous other observers. This theory assumes that there is some inherent defect in the erythrocytes. Strongly suggestive proof in favor of this is to be found in the excellent observations of Dacie and Mollison (78) and Loutit and Mollison (76). They transfused normal red blood cells into patients with congenital acholuric jaundice and noted that they survived for a normal period of 100 to 120 days. On the other hand, when red blood cells from patients with acholuric jaundice were transfused into normal recipients, they survived for only 20 to about 50 days. Their conclusions seem inescapable, namely, that the main abnormality in patients with this type of anemia is to be found in the erythrocyte itself. This view is supported also by the persistence of the abnormal erythrocytes even following splenectomy despite the relief of the clinical manifestations.

The view sponsored by Estren and Dameshek (79) holds that some toxic substance influences the red blood cells after they emerge the bone marrow as biconcave disks and causes them to assume the spherocytic shape. He points out that the erythrocytes and reticulocytes when they leave the bone marrow are normal and that certain chemical and other extrinsic agents may cause spherocytosis. An additional point which is emphasized pertains to the etiology of the crises observed in this disease. It is probable that they are due to some additional cause other than the widespread spherocytosis which is associated and undoubtedly related etiologically to this condition.

The theory of the fundamental cause of the anemia in hereditary hemolytic anemia which is in favor by most students of the disease considers it to be due to some inherent defect of the erythrocytes. The alternate view has less support but still must be considered chiefly in relation to crise of the disorder. As has been said by Estren and Dameshek (52), "Crises thus and perhaps the entire disorder itself may be due to some extra erythron abnormality specific for the patient's own red blood cells and giving rise to spherocytosis." My own personal tentative impression is that the inherent defect theory of the erythrocyte is the theory of choice at present and best explains the characteristics of the disorder. It must be kept in mind, however, that the crises are associated with some additional cause, the nature of which is not entirely clear at present and may be due to some unidentified extrinsic factor.

A third factor in the etiology is suggested by Doan (57), namely, that congenital hemolytic icterus can be considered as a type of hypersplen

ism which he defines as a hyper instability of the spleen sometimes inherited as a mendelian dominant gene factor In his opinion the hypersplenic type of events may well include abnormal stasis in the spleen calling for a compensatory increase in the delivery of the marrow elements separation of the plasma from the cells with an increase in the mechanical intercellular friction, loss of erythrocyte potassium with other electrolyte disequilibria leading to increased fragility pathologic concentration of lysolecithin and lysolecithin like, spherocyte inducing biochemicals normally produced in physiological amounts by the reticulo endothelial cells, with hemolytic blocking or other polyhemagglutinin antibodies theoretically derivable from the reticulo endothelial cells and exceptional opportunity for phagocytosis by the reticulo endothelial elements All of these many and diverse influences he considers, provide an ideal environment for the establishment of a vicious cycle of cell destruction and withholding which processes may be accelerated or slowed, depending on a variety of factors"

The etiology of hemolytic crises is considered elsewhere (see p 162)

Pathology—*The Spleen*—According to Thompson (80) the spleen in this condition usually weighs between 1000 and 1500 grams although one has been reported as weighing 3500 grams There are usually no adhesions present as there are commonly in Banti s disease and hence the organ is readily removed at operation The cut section is relatively dry and is of dark purplish red color homogenous in texture and bulges slightly above the capsule The malpighian bodies are not visible Microscopic examination characteristically shows that the malpighian bodies are small and widely separated The venous sinuses are enlarged widely dilated and frequently empty The most characteristic feature on microscopic examination is that the pulp is closely packed with red blood cells There is no increase in connective tissue or iron pigment There is only slight evidence found of phagocytosis of the red blood cells The outstanding feature of the spleen is the enormous engorgement of the pulp with erythrocytes while the sinuses are relatively empty of blood In the opinion of some authors (81) the picture in the spleen is to be interpreted as signifying a condition of hyperactivity, indicating a morbid extension of an otherwise physiologic process

The Bone Marrow—Examination of the bone marrow during the active phase of the disease uniformly shows pronounced hyperplasia of the marrow with excessive activity The predominating cell is the normoblast The fat in the marrow of the long bones such as the femur and the humerus is completely replaced with red active marrow There is also an increase in the number of myelocytes and megakaryocytes

The Liver—The liver is not usually enlarged, although in some instances it has been reported to show a slight increase in size Likewise some have reported that the Kupffer cells are numerous and increased in

number but this has not been a constant finding The hepatic and Kupffer cells may contain considerable iron pigment and this same condition may also be observed in the lymph glands and the kidneys

A common finding is the presence of bilirubin stones in the gallbladder They are reported in as many as almost 70 per cent of the patients Usually they are single but occasionally are multiple but rarely numerous They contain a preponderance of bile pigment The bile is commonly very dark and likewise contains a large amount of pigment

Occasionally ulcers of the lower part of the leg in the region of malleoli are found which are persistent and refractory to all forms of treatment except splenectomy After this procedure they usually disappear promptly At present there is no satisfactory explanation of this lesion It is of interest to note that such an ulceration of the leg is relatively common in sickle cell anemia which has many features similar to chronic hemolytic jaundice

Symptoms and Signs—General Description of the Clinical Syndrome —The clinical manifestations of chronic hemolytic jaundice are exceedingly variable and in accordance with their intensity they may be classified as 1 latent 2 chronic and 3 acute

In the latent variety there is neither jaundice or anemia and the patients have no complaints referable to the disorder The only evidence of the disease which is present is the tendency of the red blood cells to be spherical or at least they have an increased thickness and a somewhat decreased mean diameter Unless the blood of such patients is carefully examined with the proper methods such changes will completely escape detection and hence it will be said that in some instances there is no family history of the disease when such a finding is present in some of the relatives The latent cases may become active at any time during the life of the individual from infancy to the fifth or sixth decade Also it is fairly certain that when the disease once becomes obviously active spontaneous remissions rarely occur Hence thereafter some degree of chronic anemia with jaundice is likely to persist throughout life unless a splenectomy is done

The chronic phase of the disease is said to be present when there is definite but slight jaundice and a mild to moderate anemia To such patients may be applied the characterization which originated many years ago namely that "they are more jaundiced than sick Nevertheless patients in this stage of the disease often do have complaints They are mainly referable to the fact that the jaundice is noticeable and that the usual symptoms of anemia such as weakness and ease of fatigue are present to a certain degree

The acute phase of the disease or "crises" which have been termed by the French crise de deglobulization is characterized by a sudden increase in the anemia with fever increased jaundice abdominal pain

and other acute symptoms. This aspect of the disorder will be described under the heading of acute crises in a later section.

Jaundice.—This sign is the usual presenting manifestation of the malady. It may be apparent from birth or appear in childhood, but occasionally it is not present until adult life. It fluctuates widely in intensity but rarely is more than moderate in extent. There may be a well marked lemon yellow color to the skin or body but the face usually has a buff color. Never is the greenish color of deep longstanding jaundice present. It is not associated with toxemia, pruritis, bradycardia or hemorrhagic tendency.

Urobilinogen is constantly present in the urine which as a result has a reddish yellow color. Usually there is no bilirubin in the urine unless the patient is in a crisis or there is an associated obstructive jaundice due to complicating gallstones. The bile acids and bile salts are not increased either in the plasma or urine.

The feces do not become clay colored but usually have a yellowish brown hue. There is an increase in the amount of urobilin in the feces. Normally about 100 milligrams of this material are present in the daily excretion of feces, whereas in chronic hemolytic jaundice the output may be increased to 10 to 20 times this amount or more.

The intensity of the jaundice is not necessarily dependent on the degree of anemia but is related to three factors as follows: 1, the degree of fragility of the erythrocytes; 2, the activity of the spleen; and 3, the biliary excretion function of the liver. Factors 1 and 2 are related to the intensity and rate of red blood cell destruction and in crises particularly there is a close parallelism between the anemia and the jaundice. In the chronic state of the disease, however, as Watson (82) points out, the bilirubin excretory function of the liver must be regarded as the most important, if not the sole factor, in determining the presence or absence of jaundice. He states that except during hemolytic crises jaundice and anemia are not directly related to each other; in fact there is a tendency to an inverse relationship. As evidence of this he cites the case of a 16 year old boy with the disease who had a hemoglobin of 20 per cent and an icterus index of 8. On the other hand in another one of his patients the icterus index varied between 45 and 92 while the hemoglobin ranged between 80 and 90 per cent. Watson even suggests that a sluggish bilirubin excretory function of the liver, instead of being detrimental, may actually be of benefit in tending to prevent anemia.

Splenomegaly.—The presence of a splenic tumor is one of the most constant features of the disease. It is probable that this organ is enlarged in every patient with the condition. The absence of such a finding therefore arouses legitimate doubt as to the correctness of the diagnosis of chronic hemolytic jaundice. In those rare cases in which the spleen is

not palpable it is nevertheless enlarged but not to an extent where it can be felt below the costal margin It is recognized that when the spleen is enlarged from any cause it must be increased several times its normal size before it can be palpated on physical examination In patients with congenital hemolytic jaundice the enlargement is usually such that the edge which is smooth and non tender as a rule extends 2 to 6 centimeters below the left costal margin In some instances although I have never observed this it is said that the organ is enlarged down to below the level of the umbilicus or even to the crest of the ilium In general it is true that the more severe the anemia and the jaundice the greater the splenomegaly The latter usually follows the jaundice but occasionally cases are encountered when the reverse of this is observed In cases of crises the spleen commonly becomes enlarged to a greater extent and often is tense and slightly tender

Biliary Disease —It has long been known that cholelithiasis or cholecystitis is commonly associated with chronic hemolytic jaundice Biliary complications are due primarily to an excessive production of bilirubin as a result of increased destruction of the red blood cells The bile is very dark and contains an excessive amount of pigment Gallstones are present in 60 to 70 per cent of the patients at some time in the course of their illness unless the condition is controlled by means of a splenectomy The gallstones are usually single but occasionally they are multiple rarely are they numerous The calculi are almost always dark in color and have a rough and nodular surface Chemical analysis shows that they contain more than 50 per cent of bilirubin and they should be considered therefore essentially as pigment stones

In some patients the manifestations of the anemia may be so mild that they are overlooked and the patient may have a cholecystectomy for biliary disease without the underlying cause being discovered Cholelithiasis in association with congenital hemolytic jaundice may occur at any age as cases have been reported in children as young as four and six years old More frequently however this complication is seen in patients in the fifth and sixth decades In some instances following splenectomy it has been necessary to do a cholecystectomy for the elimination of gallstones after the anemia has been controlled by means of a splenectomy In large part the cause of the gallstones is the excessive formation of bilirubin

Skeletal Changes —No special changes are present in the long bones in cases of chronic hemolytic anemia In recent years however it has been noted that changes in the skull resembling those observed in sickle cell and Cooley s anemia may be present These alterations are peculiar thickening and striations of the calvarium which give rise to the curious appearance aptly described as "hair on end" In other patients the tower skull and oxycephaly have occasionally been noticed Two ex

planations for these changes have been offered One that excessive proliferation of the elements of the bone marrow may cause a destruction of the osseous tracts which is responsible for a secondary hypertrophy of bone The other that excessive irrigation of bone with blood would cause a premature union of the cranial sutures and that this would result in a heightening of the cranium and oxycephalic deformity It is probable that the importance of the skeletal deformity in any given case is proportional to the degree of the hemolysis and the extent of the compensatory reaction of the bone marrow

Constitutional Anomalies—European observers (83) have reported changes in the physical makeup which give a certain characteristic appearance to a person with this disease This phase of the disease, however, has not been emphasized in this country Among changes which have been mentioned are the tower skull (turmschadel) (see section on skeletal changes) protruding eyes persisting pupillary membrane and other eye deformities an abnormally wide root of the nose, elevated palate prognathism and protruding teeth Severe symptoms in childhood may impair growth but this does not happen in the average patient with the disease

Leg Ulcers—These skin manifestations are not common but they have been reported and are of interest because a similar condition is relatively common in an allied disorder namely sickle cell anemia The large majority of cases with this complication are young women in the second and third decades of life who usually give a history of having had a persistent or recurrent ulcer about the ankle for a period varying from a few months to 20 years Such ulcerations are most commonly located in the region of the internal malleolus They are usually single but they may be bilateral and occasionally they are multiple The earliest manifestation according to Taylor (84) is a dusky blue area in the region of the medial malleolus which breaks down in the center and develops into a shallow erosion measuring about 3 to 5 cubic millimeters The edges are only slightly elevated and there is a moderate amount of yellowish slough A ring of bluish cyanosis or dark pigmentation surrounds the lesion A punched out appearance is found only in ulcers of long standing These lesions usually resist all form of therapy but respond promptly within several weeks after splenectomy The cause is obscure but it has been suggested that such a condition depends on some congenital defect or upon changes in the walls of the capillaries It is unlikely that it can be due to the spherical shape of the erythrocytes because this shape persists after splenectomy

LABORATORY FINDINGS

Blood—The Red Blood Cell Count, the Hemoglobin and Color Index—The level of the red blood cell count and the hemoglobin of the pe

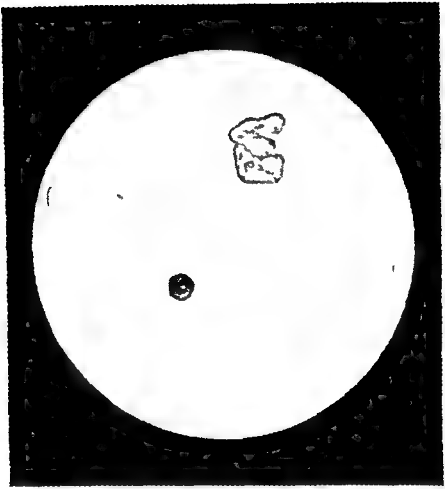

PLATE II. *Spherocytic Hemolytic Anemia*—The anemia in this patient was moderately severe as indicated by an erythrocyte count of 2 500 000 per cubic millimeter. The red blood cells are well filled with hemoglobin and many are small, round and densely colored with absent or inconspicuous central pale areas. These are spherocytes. Some of the larger cells are basophilic and a normoblast is present. Such cells afford evidence of active regeneration. The leukocyte in the upper portion of the field is a large monocyte containing a vacuole. Other laboratory findings in this patient included reticulocytosis, decreased resistance of the erythrocytes to hypotonic salt solution, hyperbilirubinemia, and increased urinary and fecal excretion of urobilin. Removal of the enlarged spleen was followed by disappearance of signs of hemolysis and recovery from anemia, although spherocytosis and increased fragility of the red blood cells were unaffected. Wright's stain. Magnification 960.

ripheral blood depends upon the stage of the disease at the time of the examination In the latent phase the red blood cell count and hemoglobin may be entirely normal or approximately so and no other abnormalities are present except spherocytosis and possibly an increase in the number of reticulocytes. In the chronic stage the red blood cell count usually varies between 3 0 and 4 0 millions per cubic millimeter and the hemoglobin between 60 and 80 per cent In some such cases however I have seen the red blood cell count remain in the vicinity of 2 0 millions per cubic millimeter with a hemoglobin of 30 to 40 per cent for a considerable period of time In a hemolytic crisis there is usually a rapid reduction in the red blood cell count which may fall to 1 0 million per cubic millimeter or less with a hemoglobin to 20 per cent or lower

The color index is usually in the vicinity of 1 0 although it may be slightly below this In some patients when there is active regeneration of blood following a crisis the red blood cells may increase more rapidly than the hemoglobin and consequently for a relatively brief interval the color index may be nearer 0 5 than 1 0

The Characteristic Changes in the Blood of Patients with Chronic Hemolytic Jaundice —The three characteristic alterations in the blood of patients with this disease are (1) the spherical shape of the cells (2) the increased fragility to hypotonic salt solutions and (3) the reticulocytosis

The Spherocytosis —The characteristic finding on examination of a stained blood film from a patient with chronic hemolytic jaundice is the presence of small round deeply pigmented red corpuscles which are called spherocytes If these are examined in a wet preparation they appear round (85) and with the micromanipulator the cells may be carefully examined and their spherical shape confirmed These spherical cells form only a relatively small proportion of the total number of erythrocytes in the blood and many of the remaining red cells particularly the reticulocytes may be considerably larger It is acknowledged by all who have investigated the matter that the spherical cells are *always smaller* than normal when the diameters are determined and also are *thicker* than normal In some instances the mean corpuscular volume is normal or occasionally increased but it may be slightly below normal The change in volume in these instances can only be explained by an alteration of shape toward the spherical Haden (1) agrees that the mean diameter of the red blood cells is *always* less than normal but the mean corpuscular volume is variable *The characteristic variation from normal however in this disease is the microspherocytosis that is the presence of red blood cells with a decreased diameter and increased thickness*

The mean corpuscular volume is most frequently normal or slightly below normal usually fluctuating between 77 and 87 cubic microns In

some cases however this measurement may be increased to 110 to 120 *cubic microns or even higher* *It is known that the reticulocytes usually* have a greater volume than the normal erythrocyte The possible explanation of whether the mean corpuscular volume is decreased normal *or increased may be found in a study of the relative* proportions of the microspherocytes the normal red blood cells and the reticulocytes in the circulating blood at any given time

Mean corpuscular hemoglobin usually varies with changes in volume Although in some instances the mean corpuscular hemoglobin concentration is elevated above normal occasionally to as high as 37 to 39 *per cent this measurement is usually within normal limits*

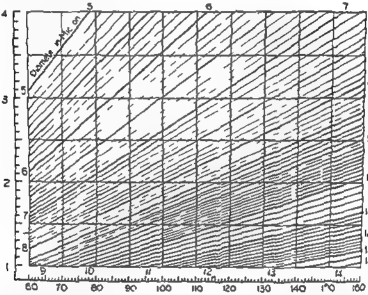

Fig 17 —Three dimensional chart for calculating the thickness of the erythrocyte from the diameter and volume by the method of von Boros To calculate the thickness the intersection of the diagonal line representing the measured mean diameter with the vertical line representing the mean corpuscular volume is determined A line drawn from this point to intersect the vertical line at the extreme left of the chart will indicate the mean corpuscular thickness For example if the mean diameter is 7 5 microns and the mean corpuscular volume is 85 cubic microns then from the figure it will be seen that the average thickness of the red blood cells is 1 9 microns (Haden courtesy *Journal of Laboratory and Clinical Medicine*)

The Thickness of the Erythrocytes—The red blood cell thickness as expressed in microns or by the volume thickness index is always increased in this condition There is no satisfactory method of actually measuring the thickness of the red blood cells but it can be calculated from the diameter and mean corpuscular volume By means of a three dimensional chart (Fig 17) prepared by von Boros *(86)* and information concerning the diameter and mean corpuscular volume the average thickness of the red blood cells may be readily determined

The volume thickness index is calculated by dividing the mean

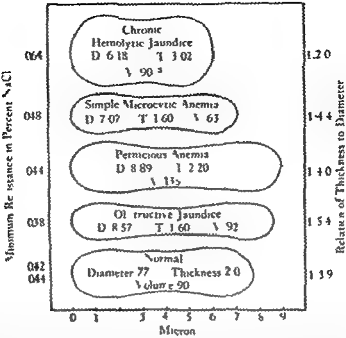

Fig 18 —Diagram showing the cross section of erythrocytes in normal persons and in those with various types of anemia D indicates the mean diameter in microns T thickness in microns V volume in cubic microns the diameter thickness ratio is expressed in the column on the right the resistence of the erythrocytes to varying dilutions of sodium chloride is shown in the column on the left (Haden courtesy *Journal of Laboratory and Clinical Medicine*)

corpuscular volume as determined by the hematocrit reading and the red blood cell count by the mean corpuscular volume as determined from the mean diameter according to the formula of von Boros (87) *This method is indicated as follows*

$$\text{Volume Thickness Index} = \frac{\text{Mean corpuscular volume as determined by the hematocrit reading and red blood cell count}}{\text{Mean corpuscular volume as determined from the mean diameter by the formula of von Boros}}$$

The index thus obtained is concerned both with the volume and the thickness and hence expresses numerically the tendency to spherical shape If the volume thickness index is greater than 1 00 then the cell is thicker than normal *in relation to diameter and volume and hence has* a tendency to assume a spherical shape If the index is less than 1 00 the cell has a thickness less than normal in relation to diameter and volume and hence is less globular than normal

Table XI from Haden (88) shows the typical cell measurements in normal persons and various anemias

Increased Fragility of the Red Blood Cells.—Increased fragility of the erythrocytes is one of the most constant findings in the blood of patients with congenital hemolytic anemia. There is convincing evidence which has been emphasized by Haden (89) to make it probable that a definite relationship exists between spherocytosis and increased fragility. In studying the characteristics of the red blood cells of different animals, he finds that those of globular shape which are natural to some species have a decreased resistance to hypotonic salt solution. This indicates that there is a direct relationship between cell thickness and the fragility of the erythrocytes. When placed in hypotonic salt solutions normal erythrocytes become progressively more globular with little change in the diameter as the solutions are made more hypotonic. It is also pointed out by Haden that in congenital hemolytic jaundice the red

TABLE XI

TYPICAL CELL MEASUREMENTS

	Volume (Cubic Microns)	*Diameter (Microns)*	*Thickness (Microns)*	*Diameter Thickness Ratio*	*Erythrocyte Volume Corresponding to Measured Diameter (Cubic Microns)*	*Volume Thickness Index*
Normal	90	7.7	1.95	4:1	90	1.00
Pernicious Anemia	135	8.89	2.20	4:1	139	0.96
Microcytic Anemia	63	7.07	1.60	4.4:1	69	0.91
Obstructive Jaundice	92	8.57	1.60	4:1	123	0.75
Chronic Hemolytic Jaundice	90	6.18	3.02	2:1	47	1.92

(Haden. Courtesy *Journal Laboratory and Clinical Medicine*.)

blood cells have at the beginning of the test with hypotonic salt solution one of the shapes through which a normal cell must pass when placed in successive dilutions of saline and hence must be regarded as nearer the hemolysis point.

From a diagnostic standpoint the fragility test is of great importance because the cells are always more fragile in typical cases. In the average patient with the disease the hemolysis begins at about 0.69 per cent and is complete at 0.39 whereas in the control the beginning hemolysis is usually at about 0.45 per cent and it is complete at 0.33 per cent. The presence of a *normal fragility* if one is sure of the test technically and the proper control procedure has been employed is strong evidence that the patient is not suffering from congenital hemolytic jaundice and furthermore in my experience it casts some doubt on the advisability of splenectomy for under these circumstances it may not be followed by satisfactory results. On the other hand the test is useful because it is

rarely positive in any other condition *except* chronic hemolytic jaundice and in some types of acquired hemolytic anemia

It should be emphasized however that there may be only slight changes in the fragility of the erythrocytes when the test is carried out in the usual manner For instance Young (68) states that in 25 patients with hereditary spherocytosis osmotic fragility of freshly drawn red blood cells was only slightly increased in seven *When sterile defibrinated blood was incubated at body temperature for 24 hours however the erythrocytes of all 25 patients showed much greater osmotic fragility than did incubated normal erythrocytes* This same observer confirms the work of Emerson Shen Ham and Castle (90) that following splenectomy the red blood cells may become slightly more resistant to hypotonic solutions but that a permanent abnormality of the red corpuscles is persistently present as determined by their osmotic fragility following incubation *It is the opinion of Young and his associates (68) that determination of the osmotic fragility in hypotonic salt solutions following incubation is of assistance in detecting otherwise uncertain abnormalities of the erythrocytes*

The mechanical fragility or the susceptibility of the erythrocytes to traumatic injury by agitation with glass beads was regularly greater in the 25 cases of congenital hemolytic jaundice studied by Young and his associates (68) and the tendency usually increased with incubation

The Reticulocytosis—This is one of the most constant features of the disease and when absent should arouse suspicion as to the correctness of the diagnosis The increase in reticulocytes in the circulating blood must be interpreted as a compensatory effort on the part of the bone marrow to produce erythrocytes in greater numbers This is an effort to replace those lost from the circulating blood by the increased destruction of red blood cells In hereditary hemolytic anemia these cells usually number between 10 and 20 per cent in the circulating blood whereas the normal number is 1 per cent or less In one patient whom I observed the reticulocyte percentage was 90 at a time when the red blood count was 1 million per cubic millimeter

Although the reticulocyte count may be increased in many different varieties of anemia and especially in pernicious anemia following treatment in no other condition is the count so persistently elevated to such a level as it is in congenital hemolytic jaundice

It is known that the reticulocytes do not account for the microcytosis as reticulocytes are usually larger than normal cells Furthermore they are not responsible for the decreased resistance to hypotonic salt solutions for microscopic examination of these cells in salt solution shows that they are the last to give up their hemoglobin

In addition to the increased number of reticulocytes there is a certain amount of polychromatophilia and cells containing Cabot's rings and

Howell Jolly bodies Normoblasts are usually present and in some cases they may be observed in large numbers

Leukocytes and Blood Platelets —During the chronic phases of the disease the leukocyte count is usually *normal or slightly increased* In crises particularly in children there is often a hyperleukocytosis with a total count exceeding 50 000 per cubic millimeter In association with such counts there is a shift to the left in the neutrophils and in some instances as many as 10 per cent of the white blood cells may be myelocytes Usually the platelet count is normal but in some instances it may be slightly increased or reduced The changes are of no particular diagnostic importance

Other Laboratory Tests —The icterus index is elevated in the active phases of the disease and is commonly found to be between 10 and 40 the higher levels being in hemolytic crises or in cases complicated by cholelithiasis The van den Bergh reaction is indirect or delayed

The urine is reddish yellow in color due to the excess of urobilin which is almost constantly present There is no bilirubin in the urine in uncomplicated cases and consequently the tests for bile are negative Bile acids and bile acid salts are not present in the urine or the blood plasma

The feces have a pronounced deep yellowish brown color and contain 20 to 30 times the normal output of urobilin

Hemolytic Crises —During the chronic course of the disease there may be mild or severe exacerbations designated crises which are characterized by variable symptoms depending on the intensity of the attack In the minor episodes there may be minimal malaise fever and increase in pallor which may persist for a few days or pass entirely unnoticed by the patient The major crises however are severe dramatic episodes which interrupt the chronic course of the disease and may cause a critical illness threatening life These are characterized by fever which may reach 102–104 degrees (F) nausea vomiting abdominal pain diarrhea and the *development* of *varying* degrees of shock with low blood pressure tachycardia and mild faintness to a complete loss of consciousness The spleen may show increasing enlargement and become tender In general the patient appears so critically ill that a fatal termination may appear imminent and does occur in some patients

In the past the condition has been considered as due to a sudden great increase in the destruction of erythrocytes In 1948 however Owren (*91*) after careful investigation of crises in 6 patients concluded that there was an acute aplasia of the erythropoietic tissues along with a maturation arrest of the granulocytopoietic tissues and thrombocytopoietic tissues In his opinion therefore the crises should be considered as aplastic rather than hemolytic in nature He has reported as have Dameshek and Bloom (*92*) and others the occurrence of crises in several members of the same family within a few days of each other

His patients were an eight year old girl her grandfather aged 59 her father aged 40 and her father s brother aged 38 years This remarkable circumstance along with others of a similar nature indicates beyond the slightest question that the occurrence of a number of cases in the immediate family within a few days of each other is not a coincidence but definitely due to some extraneous cause possibly infective

It is pointed out by Owren (91) that the changes in the bone marrow in addition to the disappearance of the reticulocytes from the circulating blood indicates that there is a complete cessation of the formation of red blood cells in the marrow This observer reports that when the red blood cells from a patient with congenital hemolytic jaundice are transfused into a normal individual they have a maximal lifetime of approximately 15 days as opposed to a life of 120 days for normal erythrocytes He calculates that if there is a sudden cessation of formation of erythrocytes in these patients the total red blood cell count in the peripheral blood will fall to one half in approximately seven to eight days and that they would be totally destroyed in about 15 days The increase in the severity of the anemia in his opinion can be explained entirely by deficient blood formation and he does not believe there is anything to indicate that these relapses result from increased hemolysis On the other hand Dameshek and Bloom (92) do not agree with Owren that the events in hemolytic crises can best be explained on the basis of an aplasia of the marrow They point out that the marrow is not aplastic and that it is capable of an extremely rapid increase in activity when splenectomy is performed Nor in their opinion does Owren s belief explain the extreme degree of spherocytosis which regularly occurs in crises and which is considered by Dameshek and Bloom to indicate a marked degree of hemolytic activity These latter observers conclude therefore that the hemolytic crises of congenital anemia are characterized by (1) an unusual degree of hemolysis and (2) inhibitory effects on maturation and delivery of the erythrocytes from the bone marrow They suggest that the occurrence of several cases in the same family over a short period of time may be explained on the basis that infection acts as a trigger mechanism which initiates an abnormal splenic process leading to crisis

The treatment of hemolytic crises is considered under the heading of treatment of congenital hemolytic anemia on page 167

Diagnosis —The essential features of congenital hemolytic jaundice are (1) the demonstration of a greater thickness of the erythrocytes or spherocytosis (2) the increased fragility of the red blood cells to hypotonic salt solutions (3) the presence of a reticulocyte percentage considerably above normal in the peripheral blood and (4) the demonstration of the disease in another consanguinous relative Coomb s test (93) is considered to be negative but there is some dissenting opinion concerning this (94) (For a full discussion of Coomb s test see page 176)

It is almost always possible to demonstrate that the cells are *thicker* than normal *or spheroidal* and study of a stained blood film usually discloses the typical microspherocytes which should suggest the diagnosis of some *type of hemolytic anemia* The red blood cells almost without fail show *increased fragility* to hypotonic salt solutions but sometimes incubation for 25 to 48 hours is necessary to accentuate this characteristic (*94*) and it also may be present rarely in other types of hemolytic anemia An increase in the *reticulocyte count* is always suggestive of a hemolytic anemia of some type These cells are usually present at levels of 10 to 20 per cent or higher a finding which is rarely observed in any other condition except pernicious anemia immediately following treatment An unequivocal diagnosis cannot be made unless it is possible to demonstrate another case of hemolytic anemia in a *consanguinous relative* especially a parent, an offspring or sibling This of course is not always possible because relatives may not be available and it cannot be said that the disease is absent from members of the family unless their blood has been examined The absence of a family history in a patient who otherwise appears undoubtedly to have hereditary spherocytosis may be explained on the basis as elsewhere stated of gene mutation low gene penetration illegitimacy and mistaken diagnosis (? acquired hemolytic anemia) (*94*)

Sometimes congenital hemolytic anemia has been confused with pernicious anemia splenic anemia erythroblastic anemia toxic hepatitis with anemia and rarely myelophthisic anemia In general it can be said that the differentiation from these diseases should not be difficult if the proper methods of hematological study are employed With routine clinical and laboratory studies however it may be *difficult to differentiate between the acquired types and hereditary spherocytosis* This is an important differentiation because the prognosis with splenectomy is better in the congenital than the acquired varieties The clinical picture the changes in the bone marrow the osmotic and mechanical fragilities and the changes in the blood may be similar in both conditions In a certain number of patients the hemolytic anemia may be of the symptomatic type in association with a dermoid cyst cancer with metastases to the bone marrow leukemia lymphosarcoma Hodgkin s disease liver disorders certain infections and tuberculosis (see section on symptomatic hemolytic anemia p 178) In others such an anemia may be secondary to certain drugs the most important of which are the sulfonamides and lead Coomb s test is considered to be positive in patients with acquired hemolytic anemia and negative in the hereditary type but Wright and his associates (*94*) found a positive test in 32 per cent (eight cases) of their patients with proved hereditary spherocytosis at a time when none of the patients were in an acute hemolytic crisis Nevertheless this procedure is considered to be useful by many observers It should be employed as a differential test and gives valuable information when correlated with the clinical findings

Treatment—Splenectomy.—There is uniform agreement among those who have studied the question that splenectomy is the only effective treatment for congenital hemolytic anemia, and that this procedure should be performed in every patient as soon as feasible after the diagnosis is established. The operative risk is low, as it is now less than 4 per cent, and it is probably even lower than this figure when splenectomy is performed by a surgeon who has had extensive experience in this field. The organ is usually not adherent or excessively large, and hence operative removal does not ordinarily present any difficulties.

There are three definite reasons why splenectomy should be performed in all patients with hereditary spherocytosis as soon as the diagnosis is established with certainty and at an early age, even in the first year of life; these are (1) because the presence of an anemia may interfere with the normal growth and development in children; (2) because "crises" which may be of a serious nature or even endanger life may develop at any time and must be considered a constant threat; and (3) eventually gall stones will be present as a complication in about 70 per cent of all patients with this disorder.

TABLE XII

N. S., NO. 190852, AGE 10—CHRONIC HEMOLYTIC JAUNDICE

Date	H.B.	R.B.C.
March 27, 1928	33	3.0
July 9, 1928	43	2.9
July 17, 1928	Splenectomy	
December 4, 1928	9	5.6
January 11, 1932	8	5.1

TABLE XII.—N. S., No. 190852. The patient, a 10-year-old girl, complained of moderate weakness, ease of fatigue, and inability to attend school regularly for several years. There had been five febrile episodes of "pneumonia" in the past few years. The patient was pale with an icteric tint and the spleen extended to the umbilicus. There was an increase in the fragility of the red blood cells; the reticulocytes of the circulating blood numbered between 9 and 18 per cent, and the white blood cells between 6000 and 10,000 per cubic millimeter. The blood bilirubin was 4.12 milligrams per 100 cc. of blood. When last seen, two years after the splenectomy, the patient had no complaints, the physical examination was negative and the blood showed no changes except a leukocytosis of 20,600 per cubic millimeter for which there was no obvious explanation.

Following splenectomy, the serum bilirubin and the urobilin excretion returns promptly to normal levels. The red blood cell count rises and the reticulocyte count falls to normal. These changes begin within a few hours after the operation and are complete within a few weeks.

There is a difference of opinion concerning the persistence of the spherocytosis. According to Thompson (85) these spherical cells persist with their attendant fragility changes for many years after splenectomy. The proportion of spherical to normal cells may be small, but

It is almost always possible to demonstrate that the cells are *thicker* than normal *or spheroidal* and study of a stained blood film usually discloses the typical microspherocytes which should suggest the diagnosis of some type of hemolytic anemia. The red blood cells almost without fail show *increased fragility* to hypotonic salt solutions but sometimes incubation for 25 to 48 hours is necessary to accentuate this characteristic (*94*) and it also may be present rarely in other types of hemolytic anemia. An increase in the *reticulocyte count* is always suggestive of a hemolytic anemia of some type. These cells are usually present at levels of 10 to 20 per cent or higher, a finding which is rarely observed in any other condition except pernicious anemia immediately following treatment. An unequivocal diagnosis cannot be made unless it is possible to demonstrate another case of hemolytic anemia in a *consanguinous relative*, especially a parent, an offspring or sibling. This of course is not always possible because relatives may not be available and it cannot be said that the disease is absent from members of the family unless their blood has been examined. The absence of a family history in a patient who otherwise appears undoubtedly to have hereditary spherocytosis may be explained on the basis as elsewhere stated of gene mutation, low gene penetration, illegitimacy and mistaken diagnosis (? acquired hemolytic anemia) (*94*).

Sometimes congenital hemolytic anemia has been confused with pernicious anemia, splenic anemia, erythroblastic anemia, toxic hepatitis with anemia and rarely myelophthisic anemia. In general it can be said that the differentiation from these diseases should not be difficult if the proper methods of hematological study are employed. With routine clinical and laboratory studies, however, it may be *difficult to differentiate between the acquired types and hereditary spherocytosis*. This is an important differentiation because the prognosis with splenectomy is better in the congenital than the acquired varieties. The clinical picture, the changes in the bone marrow, the osmotic and mechanical fragilities, and the changes in the blood may be similar in both conditions. In a certain number of patients the hemolytic anemia may be of the symptomatic type in association with a dermoid cyst, cancer with metastases to the bone marrow, leukemia, lymphosarcoma, Hodgkin's disease, liver disorders, certain infections and tuberculosis (see section on symptomatic hemolytic anemia, p. 178). In others such an anemia may be secondary to certain drugs, the most important of which are the sulfonamides and lead. Coomb's test is considered to be positive in patients with acquired hemolytic anemia and negative in the hereditary type but Wright and his associates (*94*) found a positive test in 32 per cent (eight cases) of their patients with proved hereditary spherocytosis at a time when none of the patients were in an acute hemolytic crisis. Nevertheless this procedure is considered to be useful by many observers. It should be employed as a differential test and gives valuable information when correlated with the clinical findings.

Other Forms of Therapy.—Although some have advocated liver and iron therapy, there is no convincing evidence that such forms of treatment are of value. Hence they are not recommended as useful forms of therapy in patients with this condition.

Treatment of Hemolytic Crises.—In acutely ill patients there may be a profound shock with fever and a severe anemia. The most important therapeutic indications are to replace fluid, electrolytes and red blood cells by means of blood transfusions. It is recommended that a series of two to four transfusions of 500 cc. each be given to adults by the slow drip method, which intervals of four to six hours between transfusions. To a child the same number of transfusions of 250 to 300 cc. each may be given. In the severe cases, splenectomy should follow the transfusions after a period of 12 to 48 hours depending on the condition of the patient. It is much better, however, rather than delay the operation until a severe acute crisis occurs, to do a splenectomy in the interim between the attacks when the patient is in good condition. Repeated hemolytic crisis should not be permitted to continue, for they cause long periods of chronic invalidism, and in addition they may terminate fatally.

Cortisone and ACTH.—There is some evidence to indicate that the administration of cortisone in doses of 300 mg. daily or ACTH 100 mg. daily, intramuscularly, for adults will be beneficial and this form of therapy should be kept in mind. It should be used, however, purely as a temporary measure and as a preliminary form of therapy to prepare a patient for splenectomy or in the management of acute hemolytic crisis. Our experience with ACTH and cortisone in the congenital types of hemolytic anemia is too limited to make any further definite statement at present concerning the action of these preparations in these disorders.

Unfavorable Reactions Following Blood Transfusions.—It has been emphasized for some years that blood transfusions in patients with hemolytic anemia may be followed by alarming symptoms and sometimes death, even though all care is employed in matching the blood of the donor and the recipient. With an untoward reaction there may be gradually increasing jaundice with a fatal termination, and in some patients this may be preceded by a period of anuria. This latter condition may be associated with blocking of the urinary tubules with products derived from hemoglobin released as a result of the abnormal hemolysis. Doan and his associates (97) have warned against such severe reactions and state that the most alarming symptoms occur in those patients in whom the red blood cell count is the lowest.

Although it is admitted that unfavorable reactions following blood transfusions are more likely to occur in patients with hemolytic anemia than in patients with other blood disorders, nevertheless it is known that many such patients have been given blood transfusions without the

according to this observer they have been present in patients 16 years after operation in concentrations as high as 14 per cent Lord Dawson of Penn has reported the persistence of the fragility of the erythrocytes in a woman who had undergone splenectomy over 40 years previously (95) It is stated by Vaughan (96) that following splenectomy increased fragility invariably persists but spherocytosis is lost in 50 per cent of the patients This leads her to conclude that erythropoiesis and splenic function are both at fault and that spherocytosis is not the fundamental abnormality in the disease

There are two points in regard to the operation of splenectomy in these patients which should be emphasized One is that at the time of the operation care should be taken to *explore the gallbladder region* care

TABLE XIII

E P NO 131163 AGE 22—CHRONIC HEMOLYTIC JAUNDICE

Date	*H B*	*R B C*
November 25 1925	58	3 5
October 16 1926	62	3 6
October 9 1927	0	3 8
February 4 1928	58	4 3
March 6 1928	Splenectomy	
March 30 1928	75	5 6
June 24 1934	85	5 [illegible]
January 8 1937	110	5 8

TABLE XIII—E P No 131163 This patient a 22 year-old female gave a history of having been jaundiced at intervals for five years More recently the periods of jaundice had been becoming longer and the intervals between attacks shorter She complained of very few symptoms there being only some ease of fatigue and occasional headaches She worked regularly as a graduate nurse When first seen her red blood cells showed increased fragility the blood bilirubin was elevated to 7 mg per 100 cc of blood and the reticulocytes were [illegible] per cent She gave the history that her father and one sister had been jaundiced Splenectomy resulted in a prompt restoration of her blood to normal and the disappearance of all of her symptoms

fully for stones If present the surgeon must decide as to whether a cholecystectomy should be done at the time the spleen is removed or if it is better judgment to perform the gallbladder operation at a later date Second extreme care should be taken to examine the abdominal cavity for the presence of *accessory spleens* It is known that in an occasional case such accessory organs may be present and account for the failure of splenectomy to result in a cure

The failure of splenectomy to produce the anticipated satisfactory results and restore the patient to health must be attributed to one of two conditions (1) either the patient did not have true congenital hemolytic jaundice or (2) accessory spleens were present and overlooked by the surgeon

patients with familial hemolytic jaundice however both before and after splenectomy and transfused into normal persons the red blood cells disappeared at a more rapid rate than normal This showed conclusively therefore that the abnormality in patients with hereditary hemolytic anemia was inherent in the erythrocytes On the other hand it has been shown by Loutit and Mollison (76) that red blood cells from patients with acquired hemolytic anemia when transfused into normal recipients survive normally but when normal red blood cells are transfused into patients with the acquired type of hemolytic jaundice they disappear more rapidly It is the conclusion of these investigators therefore that in the familial type there is an hereditary inborn defect of the erythrocytes and in patients with the acquired type there is a hemolytic system in action which destroys the patient s own cells as well as those which are given by transfusion

Acquired hemolytic anemia may be considered as due therefore to certain extracorpuscular factors some of which are known For example antibodies (76 29), infectious agents such as bacteria chemicals such as drugs and physical agents as burns and increased activity of the reticuloendothelial system (hypersplenism) (57)

There remains a group however clearly of the acquired type which has been designated as idiopathic acquired hemolytic anemia about which has centered a great deal of interest in recent years Such conditions may occur in the acute subacute or chronic forms There are certain sub groups which have been recognized as the symptomatic acquired hemolytic anemias in association with carcinoma sarcoma Hodgkin s disease leukemia ovarian teratoma and other disorders It is in this group of acquired hemolytic anemias not due to previously recognized extrinsic causes that the more recent work with Coomb s test indicates the importance of antibodies which destroy the patient s own red blood cells

The acquired hemolytic anemias will be discussed under the divisions of (1) Idiopathic acute subacute and chronic hemolytic anemia (2) Hemolytic anemia with erythrocyte bound antibody and (3) Symptomatic hemolytic anemia These appear to be three definite groups but it must be recognized that our knowledge is incomplete and future studies may create additional subdivisions of the three groups given above

Acute Acquired Idiopathic Hemolytic Anemia

Synonyms —Acute hemolytic jaundice of the acquired type Lederer s anemia

Definition —This condition may be defined as an acute subacute or fulminating type of anemia resulting from an increased destruction of red blood cells which is not due to the well recognized causes It is

slightest difficulty It is recommended however that when such a patient *is to be transfused the blood be administered slowly by the drip method* and that 500 cc diluted with equal parts of 5 per cent saline solution be given over a period of at least two hours If there is the slightest indica*tion of a reaction the procedure should be discontinued* at once Another worth while suggestion has been made by DeGowin and his co workers They found (98) that when the urine was alkaline the intra venous injection of a large amount of dog hemoglobin into a dog was apparently harmless When the urine was acid however the injection of hemoglobin produced renal insufficiency by obstruction of the kidney tubules with hematin which is derived from hemoglobin If transfusions are given therefore in patients with hemolytic anemia, it would seem wise, on the basis of DeGowin's work to give a sufficient amount of sodium bicarbonate to render the urine alkaline before the blood is injected *To avert all possibility of a serious reaction it is advisable in such patients to give from 50 cc to 100 cc of blood slowly and then discontinue the injection for a period of one hour* If no evidences of a reaction occur in this interval then it is permissible to proceed with the transfusion at a slow rate

Sharpe (99) has reviewed the subject of reactions following blood transfusions in patients with hemolytic jaundice and concluded that such a therapeutic measure is dangerous in the presence of a severe crisis and that it is contraindicated preoperatively and is rarely indicated post operatively

ACQUIRED HEMOLYTIC ANEMIA

General Considerations—The congenital type of hemolytic anemia *with the characteristic history and findings in the blood of other members* of the family the usual onset in early life the typical blood picture in the patient and the increased fragility of the red blood cells is a well es*tablished entity Until the initial contributions of Hayem in 1898 Widal* Abrami and Brule in 1907 and Chauffard and his pupils in 1907 and 1908 however, the acquired type was not recognized as a definite syndrome Since that time however it has been firmly established that hemolytic anemias of the acquired type do exist While they have some clinical features in common with the congenital variety they are of an entirely different etiology

It has been shown by transfusion experiments that the fundamental cause of hereditary hemolytic anemia is an *inherent defect of the red blood cell* and that the abnormality in patients with acquired hemolytic anemia is *extrinsic* in nature In 1943 Dacie and Mollison (78) studying the survival of erythrocytes when given by transfusion determined that normal blood when transfused into patients with familial hemolytic jaundice, had a normal survival period When blood was taken from

globinuria often present—fever high as a rule 2 acute with a history of about a month's illness with gradual development of symptoms and 3 subacute with symptoms of a few months duration The chronic unsuspected case with an acute exacerbation frequently cannot be separated from these types It is stated by these observers that there is no specific symptomatology associated with the disease In general the symptoms may be classified into three chief groups namely 1 those of an acute febrile illness 2 those referred to the gastro intestinal tract and 3 those attributable to the anemia The symptoms comparable to those of an acute febrile illness are an abrupt onset of extreme weakness with anorexia malaise headache restlessness and irritability generalized aches and pains and fever rising to 101–102 degrees F The manifestations of the syndrome similar to those seen in an acute gastro-intestinal disorder are anorexia nausea and vomiting pain in the splenic area mild sense of pressure in the epigastrium and diffuse and vague abdominal pain The symptoms of an anemia are weakness ease of fatigue dyspnea on exertion palpitation and sometimes edema of the ankles Often there is a yellowish tint to the skin and sclerae which may be of such a degree as to be classified as a distinct jaundice in some patients Occasionally the patient may have noticed that the stools are usually dark in color which is due to the increased excretion of urobilin In the fulminating cases the urine may be red due to hemoglobinuria

Physical Examination —Some patients when they are first seen have a striking pallor with a slightly icteric tint and appear to be severely ill *Fever of a variable degree is almost always present varying from* 99 to 103 degrees F Invariably the pulse rate is accelerated and may reach 130 to 140 per minute the pronounced tachycardia being dependent on two factors namely the fever and anemia In the advanced cases there are striking pulsations of the neck vessels A hemic murmur is almost always present and is usually of the apical type although it is often heard also at the base of the heart The liver is frequently enlarged and *in some cases* may be felt at the level of the *umbilicus* There is an almost constant increase in size of the spleen which may occasionally fill the entire upper left quadrant of the abdomen but in most patients it is barely palpable or the edge may be felt descending two to three finger breadths below the left costal margin The remainder of the examination is usually negative although occasionally slight edema of the ankles may be present

Laboratory Examinations —*The Blood*—In many cases there is a profound anemia with a red blood count which varies from 1 0 to 1 5 millions per cubic millimeter and a hemoglobin which is between 25 to 35 per cent of normal As Dameshek says The rapidity of drop in red cell count is at times so precipitous that it seems incredible The nature

characterized by an increased excretion of urobilinogen in the stools and an excess of bilirubin in the circulating blood signs of active formation of the red blood cells and a normocytic normochromic anemia of varying degree In the opinion of some it is due to the action of auto hemolysins Treatment with ACTH and cortisone and blood transfusions are often helpful and some patients may be cured by splenectomy

Etiology —One must be careful 1 to exclude all known causes of hemolytic anemia 2 to be convinced that the condition is not an exacerbation of familial hemolytic jaundice and 3 that it is not identified with either the paroxysmal or nocturnal hemoglobinuria

Dameshek and Schwartz (29) have championed the idea that these types of anemia are due to the presence of hemolysins in the blood of the patients This view is based on the observation that in two of their first four cases it was possible to demonstrate serum iso hemolysins of high titer A unique feature of this hemolysin was its ability to hemolyze cells of O group and its own blood group Furthermore they claim that similar syndromes were experimentally produced by the use of a hemolytic serum immunology comparable to that found in their clinical cases They consider that it is not improbable that the hemolysins of various types and in varying concentrations are responsible for the different varieties of hemolytic disease (A consideration of the pathologic physiologic and a further discussion of the mechanism of the production of the hemolytic anemia will be found on page 141 under the heading Physiologic and Pathologic Methods of Destroying Red Blood Cells in the Body)

Pathology —The spleen may show one of the following three types of lesions according to Dameshek and Schwartz 1 multiple areas of thrombosis and infarction 2 histiocyte proliferation often with erythrophagocytosis and giant cell formation and 3 congestion of the pulp The organ is usually enlarged from 1½ to five times its normal size The *bone marrow shows extreme normoblastic hyperplasia* and is easily differentiated from the megaloblastic marrow of pernicious anemia The leukocytes of the marrow show no abnormalities In almost all cases there is enlargement of the liver with hemosiderosis but the remainder of the organs show no constant variations from normal

Symptoms —The onset is usually less than one month before the patient has complaints severe enough to cause hospitalization although in some instances this interval may be only four or five days In about one fourth of the cases the condition has been regarded as subacute in type as the symptoms have been present for at least one month before they sought hospitalization Dameshek and Schwartz (29) make the following statement regarding the onset and course of the disease In general the nature of the disease may be listed arbitrarily as follows 1 acute fulminating—with a history of a weeks illness or less—hemo

minister blood to most patients who appear to be acutely ill Furthermore it is claimed by some that transfusions may be of value in neutralizing hemolysins which may be present *(100)*

Transfusions should be given with caution however for often there is difficulty in selecting suitable donors and careful attention should be given to the possible presence of autoagglutinins isohemolysis and the intragroup agglutinins including the Rh variety The fact that many of the red blood cells of the recipient are unusually fragile and may therefore be susceptible to hemolysis should be kept in mind It is advised *(100)* that not more than three transfusions be given in order to determine if a satisfactory remission in the condition can be obtained by this means Furthermore it is recommended that several transfusions be given prior to splenectomy They should be administered slowly It is warned that only *absolutely compatible donors* be used and that they be of the same blood group as the patient rather than employing the O type of so called universal donor Administration of ACTH or cortisone for two or three days prior to giving the blood transfusions may assist in averting the untoward reactions

It is thought by some *(100)* that if a patient does not respond to two or three blood transfusions it is unlikely that improvement will follow the administration of six or eight Also it should be kept in mind that each successive transfusion makes more likely a severe hemolytic reaction with its harmful effects on the circulation and kidneys As previously emphasized it is advisable to give a sufficient amount of sodium bicarbonate to render the urine alkaline before the blood transfusions are given and a trial injection of only 50 cc to 100 cc of blood may be given with close observation for untoward effects for one hour before proceeding with injection of the rest of the blood

There is evidence to indicate that *ACTH* and *cortisone* are of material benefit in the treatment of both acute and chronic hemolytic anemia *(101 102 103 104 105)* These preparations are not effective in patients with hereditary hemolytic anemia (hereditary spherocytosis) or in the symptomatic type of hemolytic anemia observed in some patients with leukemia Hodgkin s disease and various other conditions It has been demonstrated however that at least good temporary improvement can be accomplished in practically all patients with the acquired type and occasionally such patients may develop a long remission or perhaps a complete cure

It is recommended that all patients with idiopathic acute or chronic hemolytic anemia receive ACTH in doses of 25 milligrams subcutaneously or 75 milligrams of cortisone orally every six hours for a period of 14 days Following this period of therapy it must be decided if the patient should undergo a splenectomy which is the usual decision or continue under observation without further treatment to determine if the blood will remain continuously within normal limits

of the anemia depends to a certain extent on the number of spherocytes which are present and this is proportional to the rapidity of the development of the anemia. *The number of reticulocytes present*, which are usually larger than the average red blood cells, may have some effect on increasing the mean corpuscular volume. Hence the anemia may be microcytic, normocytic, pseudomacrocytic, or even macrocytic.

In the pseudomacrocytic type there is a high color index and an increased mean corpuscular volume but an average normal or decreased red blood cell diameter. Cells which have an increase in volume but a decrease in diameter can only be accounted for a tendency toward sphericity or increased thickness. In those patients in whom a macrocytic anemia is present, the volume and the average diameter are both increased.

In the acute cases there is usually striking evidences of increased regenerative activity on the part of the bone marrow as indicated by a *reticulocytosis, the presence of nucleated red blood cells in the peripheral blood* and a polymorphonuclear leukocytosis. White blood cell counts between 40 000 to 80 000 per cubic millimeter have been reported. There are *no important changes in the blood platelets, the count being either normal or slightly diminished.*

Urine.—The urine is usually dark, although there is an absence of bilirubin; hence the deepened color must be attributed to other pigments. It is known that urobilinogen and urobilin are usually present in increased amounts. In some patients with a great destruction of blood there is hemoglobinuria, and hence the condition may be regarded as a paroxysmal hemoglobinuria.

The Stools.—Usually the feces are highly colored. Urobilinogen in the stools is greatly increased as indicated by an output which may be *10 to 20 times or more in excess of normal. The blood serum is highly colored due to the presence of an increased quantity of bilirubin. The icterus index is usually between 25 and 35 units and the bilirubin content between 1.5 and 8 milligrams or higher per 100 cc. of blood.* The bilirubin gives an "indirect" van den Bergh type of reaction.

Treatment.—In addition to general measures there are three main points to be decided upon in regard to the management of these patients. Namely, (1) should blood transfusions be given, and if so, how many? (2) the value of ACTH and cortisone, and (3) the advisability of splenectomy.

The indications for transfusions are usually definite. Often the patient has destroyed a large proportion of his circulating red blood cells. This may have resulted in a drop to the level of 1.0 to 1.5 million red blood cells per cubic millimeter from a normal level within a few days. This means that the patient may be in a state of acute shock just as it is associated with acute hemorrhage. It is essential, therefore, to ad

minister blood to most patients who appear to be acutely ill Furthermore it is claimed by some that transfusions may be of value in neutralizing hemolysins which may be present (*100*)

Transfusions should be given with caution however for often there is difficulty in selecting suitable donors and careful attention should be given to the possible presence of autoagglutinins isohemolysis and the intragroup agglutinins including the Rh variety The fact that many of the red blood cells of the recipient are unusually fragile and may therefore be susceptible to hemolysis should be kept in mind It is advised (*100*) that not more than three transfusions be given in order to determine if a satisfactory remission in the condition can be obtained by this means Furthermore it is recommended that several transfusions be given prior to splenectomy They should be administered slowly It is warned that only *absolutely compatible donors* be used and that they *be of the same blood group as the patient rather than employing the O* type of so called "universal" donor Administration of ACTH or cortisone for two or three days prior to giving the blood transfusions may assist in averting the untoward reactions

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It is recommended that all patients with idiopathic acute or chronic hemolytic anemia receive ACTH in doses of 25 milligrams subcutaneously or 75 milligrams of cortisone orally every six hours for a period of 14 days Following this period of therapy it must be decided if the patient should undergo a splenectomy which is the usual decision or continue under observation without further treatment to determine if the blood will remain continuously within normal limits

In my opinion these preparations are useful (1) to induce a remission as a preliminary to splenectomy, (2) as a means of producing a long remission or possibly a cure in a small number of patients, and (3) and finally to make reactions less likely following blood transfusions.

The possibility of splenectomy should always be considered, although Dameshek (*100*) admits the operation carries with it a mortality of 40 per cent. It is his opinion, however, that with careful management this high rate could be lowered appreciably. Further argument in favor of the operation in the mind of this observer is once the patient has shown that a favorable response is not likely to follow the use of blood transfusions then the mortality rate may be higher.

Prognosis.—Apparently there is no accurate method of predicting the outlook in any given case. It is obvious, however, that a patient with acute hemolytic anemia is suffering from a severe illness which well might terminate fatally. In Dameshek's group (*100*) of 18 patients 10 recovered and eight succumbed to various causes, three of continued hemolysis. In a number of Dameshek's cases the effect of splenectomy was dramatic, which he thought fully justified the risk of the operation. According to this observer one must choose between a 100 per cent mortality of expectant treatment and the approximate six chances in 10 of recovery with splenectomy. He feels that it is necessary to perform splenectomy when 1 it has been adequately demonstrated that transfusions are only of temporary benefit and 2 before the patient's reserves have been completely dissipated.

The following features are listed as ominous (*100*): the presence of an unusually large number of nucleated red blood cells and myelocytes with or without associated hemosiderinuria and bilirubinuria.

In patients with acute acquired hemolytic anemia the spherocytosis, when present, usually disappears gradually following splenectomy; in fact the cells may become abnormally thin and with this the decreased resistance to hypotonic salt solution tends to disappear. This is not the case, however, in the patients with familial hemolytic jaundice and constitutes one of the differences between the two conditions.

The jaundice rapidly subsides following splenectomy and the red blood cell count and other abnormalities of the circulating blood usually reach normal within two to four weeks after the operation. According to Dameshek (*100*) none of his cases of either the familial or acquired type in whom a splenectomy was done have shown a relapse after a variable period following the operation. The first 3 cases had been, at the time of his report, operated upon 5½ years previously.

Chronic Acquired Idiopathic Hemolytic Anemia.—All agree that there is a variety of chronic acquired hemolytic anemia which differs from the hereditary type in etiology and other important respects although it may resemble it from a clinical standpoint in certain particulars. With

the ordinary clinical methods of examination it is not always possible to differentiate between the two varieties although Coombs test is considered by some to be of value for this purpose

The following additional considerations are *helpful but not conclusive* in differentiating between the two varieties These conclusions are based in part upon studies by Dr Luis Sanchez Medal of Mexico City made on a group of 45 patients at the Simpson Memorial Institute who had hemolytic anemia 14 were classified as congenital hemolytic anemia nine as acute acquired and 22 as chronic acquired hemolytic anemia

1 The active manifestations of the disease usually appear in childhood or even infancy in the congenital type and often at a much later age in the acquired variety

2 In chronic acquired hemolytic anemia there is almost always an enlarged liver or lymph glands or both whereas in the congenital types the changes are much less common

3 Spherocytosis that is the presence of microspherocytes is present in all patients with the congenital variety but such cells are not so commonly observed in the acquired type Furthermore in the former there is almost always evidence of increased fragility whereas in acquired hemolytic anemia this is present in only about 40 per cent of the patients

4 The white blood cell count has a tendency to be normal or slightly elevated in the congenital variety and there is often a leukopenia in the acquired types Furthermore in the latter there is not infrequently a few abnormal lymphocytes and monocytes

5 In our experience splenectomy has always been successful in the treatment of patients with congenital hemolytic anemia and we have not hesitated to recommend such a procedure when the diagnosis was established That such treatment is less successful in patients with the acquired type of hemolytic anemia is the opinion of all observers but there is a lack of agreement concerning the number of such patients who are *not benefited* by such an operation Our experience justifies such an operation for two reasons first and most important we have evidence to indicate that about two thirds of our patients show material objective evidence of worth while improvement following splenectomy and some have had a complete restoration of health with a return of the blood to normal It must be said however that the period of observation in some of these patients has undoubtedly been too short upon which to base a definitive statement as in some instances the interval after the operation has been less than one year Additional time is necessary therefore in order to evaluate this phase of the problem adequately but our preliminary observations are encouraging The second reason for considering splenectomy in such patients is the lack of any other type of treatment which is effective in a high proportion of cases and the knowledge that spontaneous improvement is rarely striking

6 The usefulness of ACTH and Cortisone in chronic acquired hemolytic anemia is discussed on page 173

Clinical Findings —These patients have the usual *symptoms of anemia* namely pallor weakness, ease of fatigue, dyspnea on exertion and palpitation the severity depending on the level of the hemoglobin content of the circulating blood In addition there is highly colored urine, hemolytic crises may occur the blood film *shows microspherocytes and large* reticulocytes and the bone marrow is hyperplastic There is an increase in the urinary and fecal urobilinogen In the opinion of Estren and Dameshek (*104*) the concept that they are latent cases of hereditary spherocytosis *is no longer tenable for the following reasons 1 There is* no evidence of spherocytosis in the patient s family 2 Spherocytes are not evidence solely of a hereditary trait but may be observed in various hemolytic anemias due to external agents 3 There are certain immunohematologic *differences between these cases and definite cases of heredi*tary spherocytosis 4 Splenectomy less constantly produces favorable results 5 If a complete cure is effected by splenectomy the red blood cells revert completely to normal that is spherocytosis does not persist *These observers believe the cause of the anemia in the chronic acquired* type is the presence of circulating antibodies which injure the red blood cells and permit their easy destruction that is the fundamental cause of the hemolytic anemia are antibodies arising from some unknown cause

Hemolytic Disease with Erythrocyte bound Antibody —*In 1946* Boorman Dodd and Loutit (*105*) studied the agglutination reactions of the washed red blood cells from patients with hereditary and acquired hemolytic anemia using antihuman serum rabbit serum This test was introduced *by Coombs Mourant and Race in 1945 (106) It may be described* as follows normal human serum plasma or plasma globulin is injected into a rabbit This results in the production of antibodies in the blood serum of the rabbit against human protein The rabbit serum thus produced *is designated as anti human serum rabbit serum antiglobulin* serum or Coombs serum This serum will react, according to the accepted antibody antigen manner specifically with human serum It would not be expected to react with human red blood cells unless human serum was attached to it It is known that Coombs serum *does not react* with *normal washed* erythrocytes But it does cause agglutination and here is the important point with the washed red blood cells from patients with certain types of acquired hemolytic anemia It is thought that such red blood cells have a coating or bound antibody globulin on them which reacts with antihuman globulin antibody prepared from rabbits immunized with normal human serum It is assumed that such red cells which are agglutinated have some human serum factor as an antibody or antibody globulin which is so intimately associated with the red blood cells that it cannot be removed by washing (*106 107*)

The classical example of such coated antibodies occurs in erythroblastosis fetalis. This is shown by the clumping of the erythrocytes of infants with this disorder when they are brought into contact with Coombs serum. More pertinent to the present discussion is the observation that when the washed red blood cells from certain patients with acquired hemolytic anemia are brought in contact with such serum they show clumping, whereas the erythrocytes from patients with the hereditary type of hemolytic anemia are said not to show this phenomenon. For example, Loutit and Mollison report (*76*) that in 17 cases of hereditary hemolytic anemia the red blood cells were *not* agglutinated with the Coombs serum, whereas in seven cases of acquired hemolytic anemia the test was positive. They suggest that the erythrocytes of patients with acquired hemolytic anemia have adsorbed from the plasma an immune antibody, whereas the red blood cells of patients with the congenital type of the disorder do not adsorb immune antibody.

In a careful study and consideration of Coombs test it is concluded by Singer and Motulsky (*108*) that by this means the presence of globulin antibodies adsorbed to the surface of the erythrocytes can be demonstrated. All of their seven cases of acquired hemolytic anemia and one case of symptomatic hemolytic anemia (reticulum cell sarcoma) gave a positive test. There was a negative result in a patient with a hemolytic anemia due to a sulfonamide drug. In seven patients with hereditary spherocytosis the reaction was negative in six but positive in one who was severely ill. Following splenectomy in their patients with acquired hemolytic anemia, either the coated spherocytes disappeared or the coated cells remained present although the abnormal hemolysis no longer continued. In their one patient with hereditary spherocytosis and a positive Coombs test there was a disappearance of the coating although the spherocytosis persisted. According to these authors, a positive test indicates the presence of immune bodies; the absence of an immunological mechanism in a patient with a hemolytic anemia suggests strongly that the condition is a familial spherocytosis if drugs and other obvious hemolytic agents can be eliminated. They urge that if the test is positive the hemolytic anemia should be designated as the "immunologic" type, but they state that such an immunologic hemolytic anemia can be found superimposed on hereditary spherocytosis.

The different reactions with Coombs antiglobulin test is important for at least two reasons: 1. it may serve as a method of differentiating the acquired from congenital types of hemolytic anemia, and this is important from the standpoint of prognosis and treatment; and 2. it provides some understanding of the mechanism of destruction of the erythrocytes in the acquired type of the disorder, namely, that the body develops antibodies which react to agglutinins and destroy its own erythrocytes.

Although the value of Coombs test has been accepted by many observers as a valuable method differentiating between the hereditary and acquired forms of hemolytic anemia this is not in agreement with the findings of Wright Dodd Bouroncle Doan and Zollinger (*109*) 1951 They report that "the current claims however for developing (Coombs) serum is a reliable diagnostic procedure have not been verifiable in our laboratory since 32 per cent of our patients (eight cases) with proved hereditary spherocytosis have shown incomplete antibodies by one or both methods" Further investigation of the Coombs test in the hemolytic anemias seems to be indicated The original studies on this reaction and subsequent confirmatory observations appear to be sound The explanation of the discordant report of Wright and his associates (*109*) is not apparent at present

Symptomatic Hemolytic Anemia

Definition —Symptomatic hemolytic anemia may be defined as a syndrome which presents a similar picture to ordinary spherocytic hemolytic anemia including changes in the blood and splenomegaly but showing a definite etiological relationship to some underlying disease usually of a neoplastic nature such as Hodgkin s disease generalized carcinomatosis and others The subject has been fully reviewed by Waugh (*110*) Watson (*111*) and Singer and Dameshek (*112*) and Estren and Dameshek (*104*)

In most instances the anemia which is associated with malignancy and metastic lesions Hodgkin s disease and leukemia is of the myelophthisic type which is either normocytic or slightly macrocytic in nature It is looked upon as due to the encroachment of the malignant cells on the red blood cell forming tissue in the bone marrow which reduces its extent and hence causes a decreased production of red blood cells and an anemia It should be emphasized that this is the usual type and the one to be expected when such conditions are encountered

That an anemia of the hemolytic variety may sometimes be observed in association with these conditions however is of importance for two reasons namely 1 because the recognition of its cause might prevent an unnecessary splenectomy in a patient who was thought to have been suffering from an acquired or familial hemolytic jaundice and 2 in certain instances, where the underlying condition is remedial such as a dermoid cyst it may present a much more favorable outlook

Extensive hematologic and metabolic studies have been reported by Craig Waterhouse and Young (*113*) in a patient with chronic lymphatic leukemia complicated by autoimmune hemolytic disease (symptomatic acquired hemolytic anemia) In this patient reduction in the number of circulating lymphocytes in the size of the peripheral lymph nodes and in the rate of destruction of the red blood cells was observed follow

ing the administration of ACTH for a period of 15 days and for a total observation period of nine months

Etiology —The association of a symptomatic hemolytic anemia has been observed in patients with dermoid cyst (teratoma) of the ovary (*112 114 111*) carcinoma of the head of the pancreas (*115*) carcinoma with metastasis to the bone marrow (*110 116 117*) lymphosarcoma (*112 118 72 119*) Hodgkin s disease (*112 120 121 122 123*) leukemia (*112 124 111 125 126*) infectious diseases (*127*) infectious mono nucleosis (*128*) in liver disease (*129 130 111 131 132*) in streptococci and staphylococcic infections tuberculosis (*133*) syphilis and those due to anaerobic organisms including B *Welchii* (*134*) Watson (*131*) in approximately seven years observed 46 cases of hemolytic anemia of which 27 were classified as the microcytic (familial or congenital) type and 21 as the macrocytic (secondary or acquired) type Of the latter group nine were associated with liver disease three with Hodgkin s disease six with leukemia one with chronic bleeding into an ovarian cyst one with hyperthyroidism and one with Banti s disease

Although hemolytic anemia may occur as a result of poisoning with lead phenylhydrazine and the sulfonamides in which spherocytosis is produced according to Singer and Dameshek (*112*) they should not be considered as belonging to the group of symptomatic hemolytic anemias

Any discussion of the cause of these anemias must take into considera tion the facts (1) that spherocytosis with increased fragility is usually present in the patients and (2) splenectomy may eliminate the disorder It is pointed out by Watson (*111*) however that the total of 15 cases of acquired hemolytic jaundice which he has reported in detail the red blood cells were at least larger and in one instance much greater in size than normal For example by employing the Bock erythrocytometer the average erythrocyte diameter in the familial group was found to range from 6 6 to 7 2 microns whereas in the acquired group it was regularly more than 8 0 microns It should be emphasized however that Watson (*111*) differentiates between a macrocytic anemia and microcytic anemia by a determination of the average diameter of the red blood cells This of course does not exclude the presence of microspherocytes Further more this observer found that two of the cases which were classified as macrocytic anemia in association with liver disease exhibited decreased resistance to hypotonic solutions of saline In one of these patients the average diameter was 8 35 microns and in the other 8 1 microns From these observations it was deduced by Watson (*111*) that increased fragility may at times occur in anemias other than those characterized by the presence of spherical microcytes There is however a possibility that the facts stated above may be subjected to a different interpretation as suggested by Dameshek and Schwartz (*135 136*) namely that the macrocytosis such as observed in the two patients mentioned may be

related simply to an increased percentage of large reticulocytes and that there still might exist an underlying spherocytosis to account for the moderately increased fragility

The underlying cause of the increased red blood cell destruction in this type of anemia is obscure It is assumed by Singer and Dameshek *(112)* that the fundamental pathological lesion either produces or stimulates the production of hemolysins It has not been shown, however that circulating antibodies exist in these cases *(104)* Since various lesions of the spleen may be associated with such a disorder it must be assumed further that this organ in some instances may stimulate *the formation of such hemolysins In those conditions associated with* an enlarged spleen the hemolytic anemia may be attributed to hypersplenism

In the case of causative lesions which are not associated with the spleen it is possible that a more indirect stimulation of the formation of these substances may occur *Certainly the exact etiological factors* regarding the cause of hemolytic anemia including the symptomatic type are obscure at present although a number of theories have been evolved This unsettled state is indicated by the statement of Singer and Dameshek which is so broad that it includes almost all of the theories which have been devised concerning the etiology of these anemias They state *(112)* it seems likely the hemolytic syndromes are due to various etiological mechanisms involving hemolysins agglutinins complement *activity, mechanical trauma, and constitutionally damaged red* cells We believe that certain disorders notably lymphatic leukemia lymphoid neoplasma Hodgkin s disease and some infectious states occasionally result in hemolytic anemia by evoking one or more of these mechanisms

Symptoms and Signs —The clinical manifestations of such disorders are a combination of those usually accompanying hemolytic anemia and the ones of the underlying causative disease Such an anemia produces pallor with a yellowish tint in the absence of bile from the urine *In most cases there is moderate enlargement of the spleen* Other signs that usually go with an increased destruction of red blood cells are a bilirubinemia with an indirect van den Bergh reaction normal or dark colored stools and almost always an increased output of urobilinogen The other findings are those usually associated with malignancy, although it should be noted that other conditions than neoplasms may be associated with this type of anemia namely infections liver disease and benign ovarian cysts *It has been emphasized by Waugh (110)* that a more detailed and systematic examination of bones in cases of malignant tumors reveals a high percentage of metastases in the osseous system which may be responsible for such an anemia in some instances

The Blood —In most instances spherocytosis with increased fragility can be demonstrated by careful examination The spherocytes character

ized by their small size and dark appearance are in striking contrast to the large red blood cells containing reticulum As in all cases of hemolytic anemia there is evidence of greater regenerative activity on the part of the marrow as indicated by an increased number of reticulocytes nucleated red blood cells polychromatophilia polymorphonuclear leukocytosis immature granulocytes and an increased number of blood platelets

The bone marrow in such patients usually shows an extreme hyper plasia especially of the red blood cell forming elements

The red blood cells may have an increased mean corpuscular volume or there may be a "pseudomacrocytic anemia as indicated by an average volume of the erythrocytes which is greater than normal and a mean diameter which is less than normal This can only be accounted for on the basis that the cells are spherical in form rather than bi concave disks The color index is almost always 1 0 or more and the mean corpuscular hemoglobin concentration is usually above 30 per cent

Differential Diagnosis—When evidence of a hemolytic anemia is presented in any given patient several possibilities should be considered before the diagnosis of symptomatic hemolytic anemia is definitely ac cepted It should be remembered that this diagnosis in addition to being based on positive signs requires that certain other conditions be eliminated which might present clinical pictures simulating it very closely Singer and Dameshek (*112*) mention three groups namely (1) per nicious anemia (2) a heterogenous group of hemolytic syndromes in cluding the congenital and acquired idiopathic hemolytic anemias such conditions as sickle cell anemia Cooley s erythroblastic anemia the Marchifava Micheli syndrome of paroxysmal nocturnal hemoglobinuria and (3) the hemolytic anemias of known etiology such as those due to various drugs which should not be included in the true symptomatic anemias

In general it may be said that the diagnosis is made on the knowledge that such a syndrome may occur secondary to the various conditions mentioned often but not always malignant in nature and by the demonstration that the diagnostic criteria of hemolytic anemia are present in the circulating blood

Treatment and Prognosis—The therapy and outlook in any given case depends largely on the underlying cause of the hemolytic anemia In many cases it is neoplastic in nature and hence the outlook is hopeless It should be remembered however that the cause may be a benign con dition such as an ovarian cyst and its removal may be followed by a com plete restoration of the blood to normal The following case is illustra tive of this point (*112*)

A 47 year-old Jewish housewife had the symptoms of an anemia with slight jaundice for four months and presented the following blood picture hemoglobin 34 per cent red blood cells 1.59 millions per cubic millimeter

reticulocytes 46 per cent mean corpuscular volume 78 cubic microns mean cell diameter 6 0 microns mean cell thickness 2 8 microns Hemolysis in hypotonic salt solutions began at 0 68 per cent and was complete at 0 4 per cent The serum bilirubin was 5 0 milligrams per 100 cc The diagnosis of familial hemolytic jaundice was made although no history was obtained of other cases in the family Splenectomy was followed by a remission in the course of the disease and a return of the red blood cell count to normal for a period of about four months At this time there was a complete relapse and the *clinical picture was very much the same as prior to the splenectomy Eight months after the splenectomy* a second operation was done on the basis that an accessory spleen might be present None was found but a thick walled dermoid cyst of the ovary was removed Following this operation the patient's blood returned to normal and at the end of 20 months she still remained in good condition

This case therefore appears to be one of a symptomatic hemolytic anemia which was benefited temporarily by splenectomy and who was apparently cured by the removal of a dermoid cyst The outlook in other cases of symptomatic hemolytic anemia would also be good if the fundamental underlying disease could be eradicated such as liver disease or various infections In most instances however as the primary cause of the condition is a malignant one the outlook is ominous and the only treatment of the anemia is purely symptomatic by means of blood transfusions although often striking temporary improvement may result following roentgen therapy in patients with Hodgkin's disease lymphosarcoma, and leukemia Iron and liver extract are of no avail

Hypersplenism —The concept of hypersplenism as elaborated by Doan (*57*) and by Dameshek and Estren (*58*) has been presented elsewhere (*see page 144*) but some aspects of the state will be discussed here in *more detail*

Primary hypersplenism may be defined according to Doan (*57*) as a specific overactivity of the spleen with sequestration and phagocytosis *of erythrocytes platelets and granulocytes singly or including all three* in varying degree by the reticulo endothelial cells of the spleen This may sometime be inherited as a mendelian dominant gene factor, or as Doan says in some instances as a recessive character of infrequent expressivity It has been maintained by Dameshek and his associates (*58*) that the spleen in addition to its function of destroying red blood cells is also an endocrine organ which regulates the production of red *blood cells, granulocytes and platelets from the bone marrow*

Hypersplenism is divided into two types by Doan (*57*) (1) *primary* which he defines as a hyper instability of the spleen as stated above sometimes inherited as a mendelian dominant gene as in congenital hemolytic icterus or as thrombocytopenic purpura splenic neutropenia and splenic pan hematopenia and (2) hypersplenism secondary to other diseases It is this latter variety which might well be considered as

a form of "symptomatic hemolytic anemia" In this group are those conditions as Banti's syndrome Felty's syndrome acquired hemolytic icterus Gaucher's disease xanthomato is lymphatic leukemia myelogenous leukemia monocytic leukemia tuberculosis syphilis moniliasis Boeck's sarcoid Hodgkin's syndrome reticulosarcoma hemangioma and multiple myeloma It is the opinion of Doan (57) that in some of these conditions the spleen is secondarily involved and there develops a syndrome identical with one or other of those already described as associated with primary hypersplenism in which there is the sequestration and compensatory bone marrow hyperplasia but no family history of such a trait Hemolytic crises may occur also in the secondary type and threaten the life of the patient independent of the primary disease from which the patient is suffering Doan believes that when such circumstances prevail splenectomy is indicated

Hypersplenism has also been divided into two groups by Estren and Dameshek (*104*) as follows (1) idiopathic hypersplenic hemolytic anemia in which there is enlargement of the spleen of unknown causation and in which the enlarged spleen is hyperactive and (2) secondary hypersplenic hemolytic anemia in which a previously enlarged spleen suddenly becomes hyperactive According to these observers the latter variety should probably be included in the symptomatic hemolytic anemia group in association with Hodgkin's disease Boeck's sarcoid and other disorders in which the spleen is already enlarged as a result of the underlying disease and from unknown causes rather suddenly becomes hyperactive They believe also that in all probability the hemolytic anemias seen in association with splenomegaly such as chronic malaria chronic rheumatoid arthritis and infectious mononucleosis should be included in the latter group

Diagnosis of Hypersplenism —The diagnostic criteria of hypersplenism according to Kracke and Riser (56) are as follows (1) a spleen which is clinically enlarged the single exception being in some cases of idiopathic thrombopenic purpura (it should be kept in mind however that the spleen must be about 4 times its normal size before it can be palpated) (2) depleted cell values in the circulating blood causing an anemia neutropenia or thrombopenia or combinations of these (3) demonstration of a normal or hyperplastic bone marrow and (4) evidence of splenic hyperactivity by the epinephrine test The value of the latter procedure is questioned by Dameshek and Estren (58) who state that it has not been helpful in their experience as adrenalin acts on the lymph nodes marrow and liver as well as the spleen and similar results are obtained pre and post splenectomy and furthermore the mechanism of the results produced by the test are uncertain

Treatment of Hypersplenism —It is recommended by Doan that when the diagnosis of primary hypersplenism has been established and the

bone marrow eliminated as a contributing factor prompt removal of the spleen and all accessory *splenic tissue provides the only assurance of* a complete and lasting hematological and clinical remission *In second*ary hypersplenism with hemolytic crisis splenectomy is indicated and may and sometimes must be undertaken The contraindications according to this observer may be sharply defined and clearly stated" They are (1) any acute or chronic bone marrow damage (2) myelofibrosis (3) osteopetrosis in which the splenomegaly usually reflects ectopic hematopoiesis (4) panmyelophthesia and (5) ectopic splenic hematopoiesis plus secondary type of splenism

According to Dameshek and Estren (58) splenectomy is indicated in patients with hypersplenism under the following conditions it is urgent in acute idiopathic thrombopenic purpura and hemolytic crisis, it is not urgent but essential in most cases of idiopathic thrombopenic purpura familial congenital spherocytosis splenic neutropenia splenic pancytopenia hypersplenism secondary to known benign causes as rheumatoid arthritis Gaucher's disease splenic cysts tumors and abscesses and it is possibly valuable in certain Mediterranean and sickle cell anemias with excessive hemolysis certain cases of *leukemia and lymphoma with symptomatic hemolytic anemia* and in some cases of congenital hypoplastic anemia Splenectomy is contraindicated according to these observers in absolute sclerosis of the marrow as in *myeloid metaplasia of the spleen* in the great bulk of the cases of leukemia and *lymphoma* and fairly definitely in paroxysmal nocturnal hemoglobinuria Mediterranean and sickle cell anemia subacute bacterial endocarditis malaria and kala azar

Indications and Contraindications for Splenectomy —*In summary* the *indications for splenectomy are as follows*

1 Hereditary spherocytosis in which the successful results are almost 100 per cent

2 In idiopathic thrombocytopenic purpura in which there is a return to normal clinically and hematologically in between 65 and 80 per cent

3 In acquired hemolytic anemia in which approximately 50 per cent of the patients are cured

4 In splenic neutropenia

5 In splenic pancytopenia

6 *In Banti's syndrome provided there is not cirrhosis of the liver*

7 It should be given consideration in secondary hypersplenism due to benign causes such as Gaucher's disease cysts tumors and abscesses of the spleen and Felty's syndrome (*splenic neutropenia and rheumatoid arthritis*)

8 In my opinion cases of secondary hypersplenism associated with Hodgkin's disease leukemia and lymphosarcoma may be benefited temporarily but the results are not of sufficient extent or duration to warrant splenectomy

The contraindications for splenectomy are (1) the presence of any type of acute or chronic bone marrow damage (2) myelofibrosis (3) osteopetrosis in which the splenomegaly usually is due to extramedullary hematopoiesis and (4) in panmyelophthisis In addition the statement is made by Dameshek and Estren (*104*) that splenectomy is contra indicated in absolute sclerosis of the bone marrow as in myeloid meta plasia of the spleen in the great bulk of cases of leukemia and lymphoma and fairly definitely in paroxysmal nocturnal hemoglobinuria Mediterranean and sickle cell anemia subacute bacterial endocarditis malaria and kala azar

Acute Hemolytic Anemia Due to the Sulfonamide Drugs —It is known that an acute hemolytic anemia may be associated occasionally with the administration of some of the sulfonamide drugs This has been observed following the use of sulfanilamide (*137 138 139*) sulfapyridine (*140 141 142*) sulfathiazole (*141 143*) and sulfadiazine (*139 141 144*)

The condition is said to occur in 2 to 4 per cent of all patients who receive sulfanilamide therapy (*137*) but this appears to be an over estimate judging from my own experience When one considers that even small amounts of the drug may induce the condition and when the widespread use of this form of medication is taken into account it would seem to be more properly classified as an infrequent complication It occurs more frequently following sulfanilamide and lowest with sulfadiazine therapy Experience has shown that all sulfonamide compounds may produce a a hemolytic anemia and information is available which indicates that the mortality is from 5 to 10 per cent in the reported cases (*145*)

This complication is likely to follow the administration of relatively small amounts of the sulfonamide drug For example in the four cases reported in detail by Fox and Ottenberg (*138*) the amounts given were 24 12 11 and 17 grams respectively of either sulfanilamide of sulfapyridine over a period of two to three days The patient reported by Layne and Schemm (*146*) was given 39 grams of sulfadiazine in nine days an amount which surely could not be considered as excessive A case has been reported by Ross and Paegel (*145*) in a four year old child who developed a hemolytic anemia following the administration of 0 75 gram of sulfadiazine some of which had been lost by vomiting shortly after ingestion They thought that the patient had been sensitized by taking the drug two years previously

Boyer (*147*) reports the case of a 65-year old woman with hypertension and congestive heart failure who developed either a pneumonitis or multiple infarcts of the lung and to whom sulfadiazine was administered She had never previously taken any of the sulfonamides Two days after this medication had been begun the red blood cell count fell from 4 2 to 2 2 millions per cubic millimeter but there were no alarming clinical manifestations to warn of the development of this serious acute anemia

bone marrow eliminated as a contributing factor prompt removal of the spleen and all accessory splenic tissue provides the only assurance of a complete and lasting hematological and clinical remission In secondary hypersplenism with hemolytic crisis splenectomy is indicated and may and sometimes must be undertaken The contraindications according to this observer may be sharply defined and clearly stated" They are (1) any acute or chronic bone marrow damage (2) myelofibrosis (3) osteopetrosis in which the splenomegaly usually reflects ectopic hematopoiesis (4) panmyelophthisia and (5) ectopic splenic hematopoiesis plus secondary type of splenism

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generally considered to be associated with allergy a view which is suggested by the time of appearance of the syndrome and because small doses may precipitate the symptoms Attention should be directed to the fact however that none of the other drugs known to produce drug allergy are responsible for a hemolytic anemia Furthermore it is emphasized by Fox and Ottenberg (*138*) that drug fever and skin rashes which are complications of sulfonamide therapy more readily attributable to drug allergy are not associated with hemolytic anemia

It is pointed out by Layne and Schemm (*146*) that previous observers (*144*) have noted the presence of reversible cold hemagglutinins in the plasma of patients who developed an acute hemolytic anemia following the use of sulfadiazine or sulfathiazole Also in the case of atypical pneumonia reported by Layne and Schemm (*146*) such an agglutinin occurred in the plasma following treatment with sulfadiazine Although many patients with atypical pneumonia were found to have cold agglutinins a very large percentage of them had not received sulfonamide therapy The relationship between cold agglutinins sulfonamide therapy and acute hemolytic anemia which is sometimes associated at least in atypical pneumonia is not clear at the present time and further observations are necessary in order to evaluate properly the etiologic significance of these two factors in this type of anemia In a review of the etiologic factors by Ross and Paegel (*145*) it is concluded that cold agglutinins which have been reported are more likely due to the disease for which the drug is given than to the drug itself They do not believe the evidence indicates that the erythrocytes are trapped in the spleen and destroyed or that agglutinating antibodies are present in the patient s own serum It is their opinion that the hemolysis results from chemical action of the sulfonamide or some abnormal metabolite directly on the erythrocyte itself In other words they believe that as in the case of hemolysis due to phenylhydrazine and snake venom there is direct action on the red blood cells by the sulfonamide which causes injury and the increased tendency to hemolysis They consider that it is some abnormal metabolite of sulfadiazine rather than the drug itself which produces changes in the erythrocytes during the acute hemolytic attack

A mild anemia in rats (*149*) and mice (*150*) has been produced experimentally by the administration of sulfanilamide and allied compounds This supports the view held by Watson and Spink (*150*) that a slight anemia is not uncommon in persons receiving such drugs In my own experience this variety of anemia has not been encountered frequently and when present has usually been so slight as to be without clinical significance In no way does it resemble the acute fulminating and not infrequently fatal variety of hemolytic anemia

Fox and Ottenberg (*138*) contend that the acute hemolytic anemia is not due to the formation of oxidation products by the sulfonamides for

It is not clear from the report as to how much sulfadiazine had been given when the anemia developed, but it could not have been a large amount for the total dosage over a period of four days was only 16 grams. This author reports that 250 patients had been treated with sulfadiazine in the Massachusetts Memorial Hospital before such a complication was observed. According to him this affords a rough estimate of the incidence of acute hemolytic anemia but it suggests that it may be no less and possibly is somewhat more frequent following sulfadiazine than sulfathiazole therapy.

In general it may be said that the anemia develops within two to three days from the time the drug is first administered and the maximum fall in the hemoglobin and red blood cell count is likely to occur within five to seven days.

Hemolytic anemia usually appears following the administration of promin, a glucoside derivative of 4,4-diaminodiphenyl sulfone which has been used in the treatment of tuberculosis. According to Hall and his associates (*148*) when daily doses of 3.2 grams are given orally for a period of eight to 10 days, hemolysis commonly develops accompanied by anemia, leukocytosis and thrombocytosis. When the doses given during the initial period of administration are relatively small, tolerance is sometimes acquired which was interpreted as a state in which regeneration of erythrocytes was stimulated to such an extent that anemia either failed to develop or was minimal. These observers noted that when the drug was discontinued the blood values returned promptly to normal without evidence of residual harmful effects on the hematopoietic system. One of their patients had an extremely severe anemia as indicated by an erythrocyte count of 900,000 per cubic millimeter after 1.6 grams of promin had been administered daily for three days. When this drug was discontinued, recovery was spontaneous.

Pathology.—In those patients who succumb to the disease, there is found the anticipated changes of acute hemolysis. The case reported by Fox and Ottenberg (*138*) was observed to have icterus, marked swelling of the liver with striking enlargement of the Kupffer cells which contained nuclear debris and red blood cells. The hepatic cells themselves were not diffusely damaged but scattered foci of four to five necrotic liver cells were present and it was thought that these might have been due to small capillary blockages associated with Kupffer cell proliferation. The spleen in the case reported by these observers weighed 480 gms. and there was evidence of a tremendous degree of active hyperemia. Its appearance was indistinguishable from the spleen of hemolytic anemia due to other causes. An immense number of hemoglobin casts, chiefly in the deeper tubules and Henle's loops, were found in the kidneys.

Mechanism of the Hemolysis Due to the Sulfonamides.—The precise process of destruction of the red blood cells is not known. It is most

The blood changes are similar to those observed in any type of acute hemolytic anemia namely a rapidly developing normocytic or microcytic normochromic anemia The red blood cell count may fall to as low as 1 0 million cells per cubic millimeter and the hemoglobin to 20 to 30 per cent of normal Associated with these changes there is a great stimulation of the bone marrow as indicated by an increase in the number of reticulocytes and normoblasts in the circulating blood In addition there is usually an elevation of the leukocyte count often in the vicinity of 25 000 to 30 000 per cubic millimeter Although some anisocytosis may be present there is slight if any poikilocytosis The platelets do not show a significant change in numbers

Treatment —The treatment after the causative drug is discontinued is to combat the anemia and the condition of shock There is no evidence that any of the usual antianemic therapeutic measures are effective in the treatment of this condition Layne and Schemm (*146*) report however that *improvement in their patient s condition did follow the administration of 90 units of liver extract on two consecutive days but evidence that the therapy was responsible for this is not conclusive*

Blood transfusions have usually been given but there is not unanimous agreement that they are beneficial It is thought that (*138*) they are of no great benefit possibly because of further hemolysis of blood Certainly if blood transfusions are contemplated they should not be administered until all of the criteria of satisfactory cross matching has been meticulously satisfied It is undoubtedly true that *plasma transfusions* are of benefit in treating the condition of shock They are not associated with the possible danger of hemolyzing the donor s red blood cells

On the basis that death associated with anuria due to deposition of hemoglobin in the kidney tubules may occur it would undoubtedly be wise to alkalize the patient s urine and give a small (50 cc to 100 cc) trial blood transfusion if subsequent transfusions are contemplated

Prognosis —The development of an acute hemolytic anemia during the course of sulfonamide therapy is a most serious complication which might well result in the death of the patient In nine cases seen during an interval of one year by Fox and Ottenberg (*138*) there were six deaths

It is stated by Ross and Paegel (*145*) that death has occurred in 5 to 10 per cent of all reported cases of hemolytic anemia following sulfonamide therapy hence this complication must be regarded as a serious one These authors also emphasize that sulfonamide therapy should *never be given again to a patient who has previously shown a hemolytic reaction* They state however that it is not certain whether a different sulfonamide compound can be given without precipitating acute hemolysis All evidence indicates that the risk of the patient developing another attack is great and it may be more severe than the initial one

The cause of death has been regarded as due to renal blockage resulting from obstruction of the tubules by precipitated hemoglobin as

while these may be present in the blood they are not toxic *per se* Nor do these authors consider that an increased fragility to sodium chloride solutions is of significance in the causation of this variety of anemia

Symptoms and Signs—The condition usually manifests itself within a few hours to a few days after the drug therapy has been instituted With the rapid development of the anemia, there is fever chills, nausea and vomiting abdominal and lumbar pain and tenderness jaundice and in some cases hemoglobinuria Evidences of shock such as tachycardia fall in body temperature cold clammy condition of the skin hypotension and pallor in combination with the jaundice become apparent depending upon the severity of the process

The amazing rapidity with which the anemia develops is shown by the fact that the red blood cell count may fall from normal to as low as 1 0 per cubic millimeter within a few days Consequently the blood plasma may become exceedingly dark in appearance and hemoglobinuria is not uncommonly present It is estimated by Fox and Ottenberg (*151*) that in *this variety of anemia the amount of hemoglobin which is liberated* corresponds to 495 to 763 grams within a very short time If this quantity of hemoglobin were released in the blood plasma as a result of hemolysis at one time it is obvious that a very large amount of *hemoglobin would be free in the plasma*

In their experience never was more than 4 per cent of the hemoglobin excreted in the urine The hemoglobin which is retained is converted in part to bilirubin which in turn is present in such amounts as to over load the liver This is not surprising as the normal liver excretes in 24 hours as bilirubin only that amount which is derived from 12 5 grams of hemoglobin although it is known to have a considerable reserve capacity It is considered therefore (*151*) that the jaundice in this type of hemolytic anemia is due to an excess of bilirubin formation rather than liver damage This is compatible with the observation that at necropsy in the patients there is only slight evidences of liver damage and because of the prompt disappearance of jaundice in those cases which recover

Shock is a prominent symptom and undoubtedly contributes importantly to the cause of death There can be no question but what this state is produced by the rapid hemolysis and the consequent reduction in blood volume It is estimated (*151*) that the hemolysis of two thirds of the original number of red blood cells with a resultant reduction of 30 per cent in the total blood volume undoubtedly plays a significant role in the production of shock in these patients

Blood Changes—It is of importance that spherocytosis and increased fragility have been demonstrated during the acute phase of the disorder (*145*) Furthermore it has been noted that the height of the condition is characterized by the largest number of spherocytes, and the patient improves as they diminish in the circulating blood

am inclined to agree with the view of Whitby and Britton (*156*) who demonstrated in 1933 that stippled cells are young red blood cells (reticulocytes) in which the basophilic material has been slightly altered by lead. I also concur with their opinion (*157*) that an increase in either the reticulocytes, stippled cells or erythrocytes displaying diffuse polychromatophilia is indicative of red blood cell regeneration. This in turn is dependent primarily on the increased destruction of red blood cells by lead.

It has been shown by Sanders (*158*) that stippled cells in small numbers may occur in the blood of healthy industrial workers who are not exposed to lead and also that heavy exposure may be present without the occurrence of these cells. The conclusions of this observer are that an individual finding which did not exceed 5000 stippled cells per million would require additional evidence of lead absorption in order to be considered diagnostically significant. He does state, however, that if the mean stippled cell count of a group is in excess of 1000 stippled cells per million and other causes are eliminated, increased lead absorption is suggested. It is also emphasized by this investigator that either individual or group findings in excess of 9000 stippled cells per million in the absence of other known causes defines lead intoxication. I am not entirely in accord with this latter statement but would modify it to say that the findings of that many stippled red blood cells in the circulating blood suggest the presence of a hemolytic anemia of which lead poisoning is one example. On the other hand, if the mean number of stippled cells reached such a figure in a group of workmen who were exposed to lead, then the diagnosis would almost necessarily be lead poisoning.

Although there is by no means a precise correlation between the severity of the intoxication, the extent of the exposure to lead, and the number of stippled red blood cells in the circulation, there is a recognized tendency toward a prompt and progressive increase in these cells in the circulation when the lead exposure is greater. Furthermore, it is known that the number of stippled cells decrease in the blood, but with variable rapidity, when exposure to the metal is terminated. It is usual to find them restored to substantially normal levels long before the lead concentration in the blood and urine have shown corresponding decreases (*155*).

The Nature of Stippling of the Red Blood Cells.—Although stippling was first recognized by Ehrlich as early as 1885 (*159*), its relation to lead poisoning was originally pointed out by Behrend in 1899 (*160*). One of the best reviews and experimental studies relating to the origin and significance of stippling of the erythrocytes in lead poisoning is that of Key (*161*).

Three general questions have interested investigators regarding the relation of stippling to the general red cell morphology and function

described by Baker and Dodds in 1925 (*152*) and later by DeGowin and his associates (*153*). This work has been questioned by DeNavasquez (*154*) who reported that anuria developed in his cases even though the urine was alkaline and according to him there was no obstruction to the kidneys. In his opinion the anuria was associated with the hypotension of shock. The possibility that shock might be the cause of death in these patients is a very likely possibility. On the other hand it is possible that death may result from hemoglobinuria with a resultant renal insufficiency and uremia but it is likely that this would occur at a later date namely after the hemolytic condition has been present for a week to ten days or longer.

The Blood in Lead Poisoning—General Statement.—Two characteristic changes have long been recognized in the blood of patients with lead intoxication, namely 1 the presence of a mild to moderate anemia and 2 the occurrence of stippling in some of the erythrocytes of the peripheral blood.

The Anemia.—It is generally considered that the anemia of lead poisoning is hemolytic in type usually it is not severe. The red blood cell count is commonly in the vicinity of 3.0 million per cubic millimeter and the hemoglobin from 50 to 60 per cent. The anemia is ordinarily of the normochromic normocytic type with a mean corpuscular volume between 85 and 95 cubic microns and a mean corpuscular hemoglobin concentration averaging around 30 per cent. It should be kept in mind however that an anemia is not invariably present in a person who has lead poisoning. This is because although there may be a considerable increase in red blood cell destruction due to the toxic action of lead there may also be a sufficient compensatory action of the bone marrow in supplying a greater number of erythrocytes to replace those destroyed and hence an anemia may not appear. Indeed it is known that the only invariably present sign of increased red blood cell destruction as it occurs in any hemolytic anemia including lead poisoning is a greater excretion of urobilinogen especially in the stools.

It has been shown by Kehoe (*155*) in studying 30 cases during an attack of acute lead poisoning that in the red blood cell count varied between 3.4 and 5.4 millions per cubic millimeter with an average of 4.275 millions per cubic millimeter for the entire group. The hemoglobin range in these same patients varied from 8.47 to 14.9 grams per 100 cc of blood with an average of 11.4 grams.

Stippling of the Red Blood Cells.—Of traditional diagnostic value suggesting the presence of lead poisoning is the presence of stippled cells in the circulating blood. It is true that the presence of such cells should always suggest this form of intoxication when they are observed especially if the person in whom they are found is exposed to lead. On the other hand they may occur in the blood of patients with any form of hemolytic anemia of which lead poisoning is only one example. I

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They are (1) the possible relation of basophilic granulations to the nuclear or cytoplasmic substances (2) determination if these changes are the result of degeneration or regeneration and (3) the possibility that these granules are similar to other basophilic substances found in the erythrocytes namely the reticulum and polychromatophilia It is now generally accepted that the material which makes up the stippling is derived from the cell cytoplasm rather than the nucleus Furthermore the work of Key (*161*) has shown that the stippled cells are young red corpuscles which have been exposed to lead and that the granules are aggregations of the basophilic substance into small discrete masses All evidence suggests that the reaction is probably degenerative in nature

A close relationship between stippling reticulum and polychromatophilic substances has been demonstrated by Key (*161*) He has shown that stippling is not an artifact due to staining for when fresh blood from animals with lead poisoning was examined under the microscope red cells were seen to contain refractile clear masses The number of these cells corresponded roughly to those in the peripheral blood containing stippling as demonstrated by staining methods There is no evidence to indicate that the stippling is precipitated lead in the erythrocytes although it is known that stippling and precipitated lead may both be present in the same cell

The present day view is therefore that stippling should almost always be accepted as suggestive of the absorption of lead and must be considered as one of the most if not the most important diagnostic sign in lead poisoning It should be emphasized that the phenomenon is pathological in nature and develops as a result of a toxic action of the metal on young red blood cells It is of interest to note that the reaction which produces stippling must occur in the peripheral blood for regardless of how numerous stippled cells are in the circulating blood it is said that they are never present in the bone marrow (*162*) although this is disputed by others (*163*)

The Mechanism of the Anemia in Lead Poisoning —The most generally accepted view is that the anemia of lead poisoning is due to increased destruction of red blood cells in the circulating blood There can be no question but what this mechanism does play an important role but there is also evidence to suggest that there may be other contributing processes which likewise are of importance Evidence that the anemia is due in large part to the increased destruction of blood is the fact that there are increased pigments in the plasma and the bile (*164*) Further important studies dealing with hemolytic nature of the anemia of lead poisoning are those of Key (*166*)

Another finding favoring the view that increased blood destruction is the main cause of the anemia of lead poisoning is the fact that in acute poisoning either in animals or man there is every indication of an increased activity of the bone marrow which is interpreted as a compensa

tory action. Such activity is shown by the appearance of an increased number of reticulocytes, nucleated red blood cells and cells containing Howell-Jolly bodies and nuclear rings. Gould, Kullman and Shecket (165) observed the effects of acute poisoning with lead when they studied the blood of patients with cancer who had been treated with this metal. They found that as the anemia progresses during the course of several weeks the reticulocytes increased in number and normoblasts appeared. Also many of the erythrocytes, both nucleated and non-nucleated, showed stippling. Cabot rings and Howell-Jolly bodies were observed and frequently a leukocytosis was present.

The effect of lead on the red blood cells has been studied extensively by Aub and his associates (162). A summary of their findings is as follows: in vitro the exposure of erythrocytes to lead causes certain alterations on their surfaces which results in a change in the erythrocyte from an elastic distensible sac to one which is contracted, relatively inelastic and brittle. It is suggested by these workers that these changes could be explained by the union of lead with the inorganic phosphate of the cell which might take place according to the following reaction:

$$3PbCl_2 + 2Na_2HPO_4 \rightarrow Pb_3(PO_4)_2 + 4NaCl + 2HCl$$

In this manner the erythrocytes may become more brittle and are therefore more susceptible to injury. Consequently they will hemolyze in greater numbers than normal. This view receives the support of Key (166), Brookfield (167), Clowes (168) and Bhatnagar (169).

On the other hand, in more recent years a study of the porphyrin pigments and their relation to the formation of hemoglobin has brought to light information which may reveal differences between the anemia of lead poisoning and the hemolytic anemias. For example, Rimington (170) has suggested that lead inhibits hemoglobin synthesis by preventing the incorporation of iron into the protoporphyrin nucleus. When this pigment is thus liberated it appears in the urine as coproporphyrin III and it may be detected in the urine when there is no evidence of increased blood destruction as indicated in the fecal urobilinogen. Kench and his associates (170a) following a study of the blood and urinary porphyrins in lead workers have concluded that the diminution of hemoglobin in lead poisoning is a consequence not of the nonutilization of protoporphyrin but of restricted formation of this pigment.

The studies of McFadzean and Davis (163) show that stippling is readily demonstrable in the bone marrow both in the erythrocytes and in normoblasts in various stages of hemoglobination. They conclude that lead exerts its effect primarily on the nucleated red blood cell precursors in the bone marrow. This they believe causes faulty hemoglobination partially dependent on the failure to incorporate iron in the protoporphyrin nucleus. The view is also advanced that the defective erythrocytes thus produced are removed from the circulation by the spleen and

probably by the reticulo endothelial system in general They postulate that this mechanism results in a hemolytic type of anemia the severity of which varies with the intensity and duration of the lead poisoning In their opinion this view would reconcile the opinions that the anemia is hemolytic in nature with the ones which hold that it is due to faulty red blood cell formation (*170 170a 171, 172*)

Anemia Due to Phenylhydrazine and Acetylphenylhydrazine (Pyrodine) Poisoning —Phenylhydrazine was introduced into medicine for the treatment of polycythemia rubbra vera in 1918 by Eppinger and Kloss (*173*), although its use was first suggested by Morawitz and Pratt in 1908 (*174*) This drug is related to antipyrine and is a base produced commercially from aniline Acetylphenylhydrazine was initially employed as an antipyretic in the last decade of the nineteenth century Although it was known to reduce fever it was also observed to have the undesirable effect of producing a very severe anemia and hence its use fell into disrepute except for the production of experimental anemia in animals In addition to the effect on the erythrocytes it is known that the drug produces degenerative changes in the liver and kidneys Interest in acetylphenylhydrazine was again aroused by the publication of Stone Harris and Bodansky (*175*) in which it was asserted that its action was similar to that of phenylhydrazine but that it was less toxic

It is claimed by Waddell Wolff and Lanou (*176*) that pyrodine acts directly on the mature red blood cell It was suggested by these authors that a reaction occurred between the drug and the hemoglobin within the cell This they claim forms small dense refractile aggregations of insoluble methemoglobin like compounds In an experimental study reported by Bratley Burroughs Hamilton and Kern (*177*) it was determined that both of these drugs produced a profound anemia when they are injected subcutaneously into experimental animals the action being identical in the dog and the rabbit In these animals the erythrocytes assumed a motheaten and vacuolated appearance on the third day after the first injection Round refractile darkly staining intracellular bodies the so called inner bodies appeared on the following day at which time the red blood cell count varied between 3 and 4 millions per cubic millimeter Anisocytosis poikilocytosis and polychromatophilia and a rare nucleated red blood cell appeared at this time The presence of these immature erythrocytes in the circulating blood was interpreted as the outpouring of young cells from an overactive bone marrow in an attempt to compensate for the rapid destruction of blood These observers noted that acetylphenylhydrazine was more potent than the hydrochloride in its anemia producing effect and that a marked tolerance to both drugs is rapidly acquired in experimental animals They also observed that there is a rapid and extreme hyperplasia of the bone marrow and in some animals myeloid metaplasia appears in the adrenals spleen and liver Furthermore there is a striking activity of the hemolytic

system as indicated by hyperplasia of the reticular and sinusoidal endothelial cells and pronounced phagocytosis of degenerated erythrocytes and blood pigment by these elements It is known that both drugs are toxic as they may produce degenerative changes in the parenchyma of the viscera which is especially severe in the kidneys and liver

Previous workers had suggested that the phenylhydrazine compounds are strong reducing agents and split the hemoglobin into its pigment and protein fractions It is thought by some that the basic drug becomes oxidized thereby setting free a benzol ring which is the active agent in blood destruction (177)

Hence it is apparent that both phenylhydrazine hydrochloride and acetylphenylhydrazine may produce a severe anemia in animals or man by the destruction of red blood cells This action is used therapeutically to treat patients with polycythemia and thereby reduce the red blood count to normal limits The drugs are known to be toxic and if not given with due care they will produce an anemia in such patients Hence their dangers should be recognized and avoided by the careful observation of the blood of patients who are receiving them as therapeutic agents Further information concerning the therapeutic use of these preparations will be found in the section dealing with the treatment of polycythemia

In recent studies by Cruz Hawkins and Whipple (178) in which acetylphenylhydrazine was given to dogs with bile fistulae there was an output of bile pigment which corresponded closely (88 per cent) to the amount calculated to be derived from the destroyed red blood cells and hemoglobin It is suggested therefore that the drug in the doses given destroys almost all of the mature red blood cells in the circulation At the same time this massive destruction is in progress the dog was observed to produce a maximal amount of new hemoglobin and red blood cells presumably utilizing the iron and perhaps the globin from the destroyed corpuscles

The Blood in Acetanilid Poisoning —It has long been recognized that chronic acetanilid poisoning may be associated with cyanosis anorexia cachexia varied psychic and neurological disorders lassitude insomnia headache and anemia As pointed out by Herrick and Irons (179) a palpable spleen may be present in some patients Austin (180) reports the case of a 44 year old white woman who had been taking both amino pyrine and acetanilid in a headache mixture daily for 16 years It was estimated that the patient had ingested at least for a period of one month as much as $12^1/_4$ grams (0 8 gram) of acetanilid and 12 grains (0 8 gram) of aminopyrine daily The hemoglobin when the patient was admitted to the hospital was 33 per cent and there were 2 19 red blood cells and 1600 white blood cells per cubic millimeter The leukopenia was interpreted as being due to a sensitivity to aminopyrine for which there was convincing proof There were 19 per cent neutrophils The

reticulocytes numbered 20 6 per cent with an occasional normoblast The bone marrow was characterized by an increase in the number of erythro blasts

It appears to be clear that chronic poisoning with acetanilid can pro duce a hemolytic anemia of considerable extent The peculiar cyanosis which accompanies the excessive ingestion of this drug is a valuable diagnostic sign but unfortunately is not always present Although the mechanism of its production is not fully understood it is thought to be due in part to the presence in the blood of dark colored oxidation prod ucts of para aminophenol and also to methemoglobin and sulfhemoglobin (*181*) It is of interest to note that the splenomegaly which may be associated with chronic acetanilid poisoning though present for years is rapidly reversible Phenacetine (acetophenetidin) is reduced to paraminophenol as is acetanilid before exerting its typical action and hence they both have a similar effect on the blood

Arsenic Compounds Causing Hemolytic Anemia —*Arseniuretted hy drogen* (*Hydrogen Arsenide Arsine*) is a highly poisonous gas which has among other actions a hemolytic effect on the red blood cells (*182 183*)

Industries in which poisoning with this gas may occur are listed by Hunter (*184*) Included are those in which bleaching powder is made and tin refined Other industries which employ acid alloys or ores con taminated with arsenic also present this hazard

A series of such cases were described just after the first World War by Dudley a British Naval Officer (*185*) He reported that 30 men of a submarine crew of 56 were sick enough to be sent to the hospital although there appeared to be a varying susceptibility of the men to the fumes to which they all had been equally exposed Those who were more severely affected had tachycardia vomiting pain in the abdomen constipation headache tingling of the hands and feet great thirst and burning of the throat edema of the face albuminuria jaundice and a fall in the red blood cell count to as low as 1 98 millions per cubic milli meter The jaundice was due in part to increased destruction of red blood cells and to liver damage All recovered but six weeks after the acute poisoning the red blood cell count had not returned to normal The poisonous gas in the submarine was found to come from the storage batteries which were made with a lead antimony alloy containing 0 2 per cent arsenic

Three cases of acute hemolytic anemia with hemoglobinuria have been observed in fertilizer workers probably resulting from exposure to arsine gas (*186*) It is pointed out that the gas has long been known as highly toxic to man The gas AsH_3 was discovered in 1775 by Scheele Its toxic effect on the body is largely due to the fact that it hemolyzes the red blood cells The first known fatality due to it occurred in 1815 when Professor Gehlen of Munich died 10 hours after inhaling the gas in his

laboratory (*186*) The earliest industrial fatality occurred in 1873 (*186*) and most of the cases since reported have occurred accidentally in some stage of the industrial recovery of metals due to the contamination of the ore with arsenic With reference to the cause of the poisoning in the laborers in the fertilizer factory it was stated that they were employed to remove fish scrap from the holds of boats Arsenic is known to be present in fish scrap and also as a contaminant of commercial sulphuric acid which was used in the dilute form to spray over the scraps Furthermore as proof that arsenic was the cause of the anemia it was found that this chemical was present in large amounts in the urine of two of the patients

A case of hemolytic anemia following the use of *neoarsphenamine* is recorded by Young and his associates (*187*) and apparently in rare instances *other arsenical antisyphilitic remedies* may produce this condition in persons who have an idiosyncracy to these drugs

Hemolytic Anemia Due to Quinine —The case of a 42 year old woman who developed a hemolytic anemia with jaundice and a red blood cell count of 2 8 millions per cubic millimeter following the ingestion of an unknown amount of quinine for the purpose of producing an abortion is reported by Licciardello and Stanbury (*188*) The red blood cells showed variation in size and shape moderate spherocytosis and increased osmotic fragility The patient made a complete recovery after a severe illness of over a month A review of 9 cases is given by Terplan and Javert (*189*) who state that all of the cases took the drug as an abortifacient and all died with evidence of a severe degree of intravascular hemolysis and hemoglobinuria in some cases In those in whom the information was available the non protein nitrogen of the blood was high and in the fatal case reported by Vartan and Discombe (*190*) the patient in the terminal stage developed icterus and scanty black urine with a non protein nitrogen of 540 milligrams per 100 cc of blood The dose of the drug has not always been beyond the usually therapeutic dosage as small an amount as 0 4 gram proved fatal in one case The mechanism of the hemolytic process in the opinion of Terplan and Javert is not clear They state that actual intravascular hemolysis following quinine ingestion has been reported only in malaria and pregnancy

Naphthalene as a Cause of Hemolytic Anemia —Four cases of fulminating hemolytic anemia following the ingestion of naphthalene closely resembling so-called Lederer's anemia have been reported in detail by Zuelzer and Apt (*191*) They review the literature and state that a few cases have been reported in the foreign literature in which there was anemia and hemoglobinuria following naphthalene intoxication The condition apparently arises chiefly in children following accidental poisoning and in view of the availability of moth balls which consist of pure

naphthalene ($C_{10}H_8$) it may be more common than previously believed In an experimental study on dogs, the authors report that the administration of naphthalene shows that the substance is capable of being absorbed and producing an anemia of hemolytic type They observed the following order of events in dogs after the ingestion of naphthalene the appearance of Heinz bodies preceding a sharp drop in hemoglobin hematocrit, and red blood cell values fragmentation of the erythrocytes, a leukocytosis and reticulocytosis and subsequently the restoration of the blood to normal after ingestion of the chemical was stopped It is their opinion that the material causes hemolysis in vitro by direct action on the cell membranes The treatment obviously does not include splenectomy and hence an accurate diagnosis is of great importance The treatment is the administration of blood transfusions and the use of alkalies in the presence of hemoglobinuria

Antihistaminic Drugs as a Cause of Hemolytic Anemia —Three cases of hemolytic anemia have been reported by Crumbley (*192*) which were associated with the ingestion of antihistaminic drugs In one patient, the red blood cells fell to a level of 2 1 per cubic millimeter and the hemoglobin to 5 2 grams per 100 cc following the daily ingestion of 150 milligrams of diphenhydramine hydrochloride a benzhydryl ether, for a preceding 10 month period A second patient had a red blood cell count of 3 5 per cubic millimeter and a hemoglobin of 8 5 grams per 100 cc after a dosage of 150 milligrams daily of tripelennamine for the preceding 15 months A third patient received diphenhydramine hydrochloride 150 milligrams per day for about eight weeks and then developed an anemia of 3 7 red blood cells per cubic millimeter and a hemoglobin of 9 2 grams per 100 cc All three patients recovered in several months following discontinuance of the antihistaminic drugs The author concludes that since three cases of hemolytic anemia have been observed to occur in association with the use of antihistaminic drugs they should not be administered without adequate medical supervision

Other Causes of Hemolytic Anemia —During World War I it was recognized that *trinitrotoluene* could be responsible for the production of a hemolytic anemia (*193*) with jaundice and fragmented and polychromatophilic red blood cells in the circulating blood

Dinitrobenzene and other nitro aniline compounds may account for severe grades of hemolytic jaundice (*182*) Such substances are employed largely in the dye and munition industries The following to which reference has not been made are known to cause such an anemia An experimental hemolytic anemia in animals may be produced by feeding *onions* the active principle of which is *allyl propyl disulphide* (*194*) Saponin has long been employed as a method of producing hemolytic anemia experimentally (*195*) *Colloidal silver,* in part at least

causes an anemia as a result of hemolytic action (*196*) *Methyl chloride* which is employed in refrigerators for home use has been reported as responsible for hemolytic anemia (*197*) *Benzol* while it is generally known as an agent which produces an aplastic anemia is now also recognized as a chemical that may cause red blood cell destruction (*198*) Additional agents which have been listed as causes of a hemolytic anemia are as follows *dinitrobenzol anilin* and other *compounds of phenol benzol* and *toluol* (*182*) *potassium chlorate* (*199*), *benzedrine* (*200*) *phenothiazine* (*201*) *pamaquin* (*202*) *myanesin* (*203*) *phosphorus, xylene dinitrobenzene mononitrobenzene* (*204*) *toluylene diamine* (*205*) *cresol* (*206*) *diaminodiphenylsulphone* used in the treatment of leprosy (*207*) *lysolecythin* which is derived from lecithinase a result of conversion by lecithinase contained in some snake venoms (*208*), and ricin derived from the castor bean (*209*)

Snake venom has been shown to produce a hemolytic anemia experimentally and following snake bite This aspect of its toxicity was studied many years ago by Flexner and Noguchi (*210*) and others Bethell and Bleyl (*211*) produced microspherocytosis and hemolytic anemia in dogs by the injection of the venom of Crotalus atrox (Texas diamond back rattlesnake) They observed that a few minutes following the injection of either large or relatively small amounts of venom the erythrocytes showed evidence of swelling and change from the biconcave to a more nearly spherical shape A decrease in the mean cell diameter and an increase in the mean thickness was observed which indicated that the erythrocytes had assumed the shape of microspherocytes Greatly decreased resistance to hypotonic salt solution occurs which is an additional characteristic of such cells By the reported administration of doses of venom too small to produce evidence of vascular damage it has been possible to induce hemolytic anemia accompanied by hyperbilirubinemia and reticulocytosis They regard this experimental anemia as analogous to familial hemolytic icterus with respect to the changes observed in the circulating red blood cells According to them these studies support the view that spherical and "fragile" erythrocytes characteristic of the latter condition do not represent an inborn error in the formation of erythrocytes but rather an alteration in shape and resistance which occurs after their release into the circulation

FAVISM

Favism (fabism fabismus) is a condition characterized by a rapidly developing hemolytic anemia hemoglobinuria and jaundice due to the ingestion of the seeds or inhalation of the pollen of the flowers of Vicia fava commonly know as the fava or "broad" bean Reviews of this subject are by Luisada (*212*) and Mcgraith Andrews and Gall (*213*)

Etiology —The malady at present is limited largely to the inhabitants of the Island of Sardinia although it has been observed in Sicily and on the mainland of Italy Up to May 1941 there had been only three cases reported in the United States according to Luisada (*212*) The latter writer states that possibly in the future more cases may be recognized in this country because (1) of a large Mediterranean population in certain areas (2) fava beans are cultivated extensively in some states (mainly New York New Jersey Illinois and California) and (3) they are a staple article of diet in the United States being imported as canned from Italy

The attacks are rare in this country but that they do occur is evidenced by the case report of Hutton (*214*) who refers to a similar case observed by McCrae and Ullery (*215*) In Hutton s case a male age 21 fava beans *had been eaten several times in the few days preceding the attack The* onset was with sudden abdominal pain followed by the rapid development of a yellowish tint to the conjuctivae The spleen was questionably palpable the temperature 104°F the hemoglobin 32 per cent and the *red blood cell count 1 6 millions per cubic millimeter Complete recovery* within a few weeks followed the use of one blood transfusion The maternal grandmother the mother and one of the mother s brothers had *been jaundiced repeatedly Skin tests performed on the patient intra* dermally with extracts of fava beans in amounts from 0 0001 to 0 1 were negative

The attacks of favism due to inhalation of pollen occur chiefly during the months of April and May when the plants blossom those due to the ingestion may of course occur in any month The most likely theory *concerning the causation of the attack is that the symptoms are allergic* manifestations This appears to be a logical explanation as there is a short incubation period only a few individuals are effected and the condition may be initiated by extremely small doses There is a certain amount of corroborative experimental evidence in support of this The work of Demurtas (*216*) suggests the existence of different allergins and the possibility of either simple or multiple sensitizations It has been observed during an attack that the skin tests for both the flowers and seeds are usually negative for the allergin causing the symptoms but the tests for other plant parts at this time are still positive The test for the responsible allergin becomes positive during the period of convalescence

It is the opinion of Luisada (*212*) that quite probably the allergins are two one is present in the pods and seeds of fava beans and the *other is* in the flowers and in much smaller concentration in the leaves It is his opinion that they represent two kinds of differentiation from a fundamental single type *of protein Drying of the seeds reduces their* antigenic properties and prolonged cooking almost completely destroys them

There are also clinical observations which indicate that desensitization usually occurs for a short time during and after the attack for at these times patients can even digest fava bean protein without producing symptoms During life if a number of attacks are survived there may be complete freedom from them thereafter In others although a complete degree of immunity does not develop the attacks become less severe with increasing age

Pathology —The chief pathological findings as reported by Luisada (212) who based his report on a survey of the literature are as follows acute inflammation of the gastro intestinal tract and of the bronchi intense reaction of the reticulo endothelial system and normo megalo blastic hyperplasia of the bone marrow acute swelling of the spleen accumulation of white cells in the capillaries of many organs perivascular lymphocytic infiltrates venous thrombi and some degenerative lesions of the nervous centers of the kidneys and of the liver

Symptoms and Signs —The clinical picture as described by Luisada (212) is as follows the onset may be a few minutes after the inhalation of pollen but after the ingestion of the beans there is a delay of from five to 24 hours The onset is usually with dizziness which may proceed to collapse headache chills and fever The specific symptoms of the attack are 1 the hemoglobinuria and 2 the icterus The hemoglobinuria which is manifested by a red to black urine usually appears within five to 30 hours the shorter period being associated with the inhalations and the longer one when the material is ingested The jaundice appears within a few hours and usually becomes intense Fever is generally present and may reach a height of 101 to 103 on the first day Not only is the skin yellow due to the jaundice but it is also pale as the anemia develops

Laboratory Examinations —*Blood Examination* —The red blood cell count is usually in the vicinity of 1 to 2 millions per cubic millimeter and some claim that the color index is lowered There is marked leukocytosis during the first 6 to 7 days of the attack

Urine —Within a few hours after the beginning of the attack the urine shows hemoglobin which continues to be present for several days It is said that also a large amount of urobilin may be found in the urine

The Stools —Diarrhea is often present The stools may show an increase in the amount of stercobilin and in some instances there may be evidences of blood

Prognosis and Course of the Disease —When the patient recovers the hemoglobinuria and fever terminate after the fifth to the sixth day The jaundice persists for a longer period as does the anemia which may be present after a period of one month Death occurs almost never except in children and a mortality rate of 8 per cent is said to characterize the disease

Treatment.—The only therapeutic measures appear to be preventive by recognition of the nature of the hemolytic anemia and the administration of blood transfusions if the patient's condition is serious enough to warrant such a measure.

Malaria

Undoubtedly malaria is *the* most common cause of hemolytic anemia throughout the world. It is generally accepted that the major cause of such an *anemia is the increased rate of destruction of the red blood cells* which is accomplished by the parasites entering the erythrocytes. The anemia is usually of the microcytic variety and is ordinarily mild or moderate in extent as the red blood cell count is generally in the vicinity of 3.0 millions per cubic millimeter and the hemoglobin about 60 per cent.

Frequency.—The incidence of anemia due to this cause of course parallels the frequency of malaria in any given region. In a study made in Puerto Rico (*217*) it was found that in some areas on that Island 25 to 35 per cent of the population had the parasites in the blood. Furthermore Molina and Gonzales found that 70 per cent of all patients thus infected had a definite though mild to moderate anemia.

In some other parts of the world it is known that even a higher incidence of infection is present among the population and knowing that at least almost three fourths of them will have a decrease in the hemoglobin and red blood cell count below normal the great incidence of this variety of anemia becomes apparent.

According to Coggeshall (*218*) it is probable that in the entire world almost 2 million deaths annually result from malaria. In the United States malaria is most frequently observed in the southeastern states but it may occur in any locality. Sporadic cases in the United States are observed in soldiers who have been in districts where malaria is prevalent, in addicts who become innoculated by contaminated syringes used for taking narcotics and following blood transfusions from donors who have had the disease.

Cause of the Anemia.—It is known that the anemia of malaria is due in large part at least to the destruction of the red blood cells by the plasmodia which develop within them. As the parasites complete their cycle of development and enter other red corpuscles more anemia with its associated jaundice develops. Although the main cause of the anemia is the destruction of the red corpuscles there is a possibility that a depression of the bone marrow may also contribute to it to some extent. This will be discussed below.

It is to be expected that an anemia would develop in patients with malaria as the disease is due to a parasite which is dependent on the erythrocytes for its existence. It has been estimated (*219*) that in order to produce symptoms there must be one parasite to every 100 000 red

blood cells Furthermore a single paroxysm may result in the destruction of a sufficient number of red blood cells to reduce the total count 1 000 000 per cubic millimeter

The Mechanism of Hemolysis —The destruction of the erythrocytes in malaria is largely intracellular and occurs in the following manner as described by Farley and Bromfield (220) Effete or damaged corpuscles are directly removed from the circulation by the phagocytic action of the reticulo endothelial cells The hemoglobin is liberated intracellularly converted into globulin and hematin which in turn is split into hemosiderin containing iron and bilirubin The latter is responsible for the indirect van den Bergh which normally does not exceed 0 5 milligram per cent it is removed from the circulation and converted by the polygonal cells of the liver into bile pigment but is never secreted in the urine With increased blood destruction a hyperbilirubinemia ensues sometimes with jaundice depending on the amount of the material in the circulating blood also highly colored stools and urobilinuria results

When free circulating hemoglobin is present in the blood stream it is known to be treated as a foreign protein and is taken up by the reticulo endothelial cells and also is dealt with by the parenchymal cells of the liver and kidneys When a sudden lysis however produces a large amount of free hemoglobin this is likely to exceed the renal threshold of the substance Consequently a portion is excreted by the kidneys and a hemoglobinuria results Apparently this occurs in Blackwater fever

In an extensive study (220) on spontaneously occurring malaria and a certain number of cases in which the disease was employed as a therapeutic agent for the treatment of syphilis of the nervous system the following conclusions were deduced

1 Blood destruction in malaria is largely an intracellular phenomenon

2 It is unaccompanied by hemoglobinemia but is associated with a hyperbilirubinemia

3 Following specific treatment there is a decrease in plasma bilirubin

4 Reticulocytosis follows specific treatment with great regularity and its intensity is related to the degree of anemia the maximal response occurring within six to 10 days

5 Increased blood production from the normoblastic marrow which is generally hyperplastic in nature automatically follows the destruction of the parasites and proceeds quite independently of the administration of therapeutic agents such as iron

Deductions Concerning the Mechanism of the Anemia Based upon the Behavior of the Reticulocytes —It is known that the level of the reticulocytes during an active infection is below normal or at least is not increased Within six to 10 days following treatment with quinine however a maximum rise in reticulocytes occurs which is proportional to the degree of the existing anemia In 1928 when studying the blood daily of patients

with general paresis who were inoculated with malaria for therapeutic purposes I observed this phenomenon and considered that it was indicative during the active infection of a depressing action on the marrow This if true could be regarded as another factor in the causation of the anemia

This increase in the reticulocytes following therapy for malaria has been noted by other observers among them being Fairley and Bromfield (*220*) Tareeff Epstein and Gontaeva (*221*) and others In 1934 Eaton (*222*) observed that the reticulocytes were prone to be infected by the malarial organisms hence are probably destroyed in numbers greater than normal The question arises therefore if the increased rate of destruction of the reticulocytes accounts for their normal or decreased numbers during the period of infection and for their increase after the period of specific therapy It is the conclusion of Shushan Blitz and Adams (*223*) that the reticulocytes during the period of infection are normal in numbers excluding the cases of severe anemia According to them reticulocytes are selectively infected by the tertian parasites whereas in subtertian malaria reticulocytes and mature erythrocytes are infected with equal facility They suggest that this may explain why subtertian malaria is associated with higher reticulocyte count in the peripheral circulation than in benign tertian malaria

The Effect of Antimalarial Drugs on the Erythrocytes —It is known that various antimalarial drugs sometimes have a profound effect on the red blood cells and hence may be an important contribution factor in the causation of the anemia in a patient with malaria In a review of the effect of these drugs on erythrocytes by Rigdon and Breslin (*224*), it is pointed out that apparently some of the antimalarial drugs act on the enzyme system within the red blood cells whereas others may affect the consumption and transportation of oxygen by the erythrocytes which in itself would be detrimental to the parasites It is stated by these observers that methemoglobinemia has been observed following the administration of quinine pamaquine and pentaquine and that Heinz Ehrlich bodies have been observed in erythrocytes following the administration of pamaquine Atabrine has been reported by Custer (*225*) to have been responsible for 57 fatal cases of aplastic anemia and it has been known to cause Blackwater fever (*226*) A hemolytic anemia may occur according to Rigdon and Breslin (*224*) following the use of quinine pamaquine pentaquine and throthricin These authors conclude that as many of the antimalarial drugs affect the erythrocytes directly it lends support to the possibility that their action is through the red blood cells and not by stimulation of immune reactions

Changes in the Blood in Patients with Malaria —About 70 per cent of the patients with malaria have a macrocytic or normocytic anemia of mild or moderate extent and approximately one third have a leukopenia

There is nothing in the blood picture which in itself would be diagnostic of malaria apart from finding the causative organism

The blood studies of Molina and Gonzales (217) on 100 patients in Puerto Rico 83 per cent of whom had chronic and 17 acute infections give a good idea of the incidence and nature of the anemia encountered in this disease in that region Seventy per cent of the cases had a red blood cell count below 4 million per cubic millimeter but only 10 per cent had hemoglobin levels below 10 2 grams (70 per cent) The degree of anemia for the entire group was slight the average red blood cell count being 3 95 per cubic millimeter and the hemoglobin 12 30 (85 per cent according to the standard that 14 5 grams per 100 cc of blood is equal to 100 per cent) The erythrocyte counts varied between 5 70 and 1 98 cells per cubic millimeter whereas the hemoglobin ranged from 7 25 (50 per cent) to 16 1 grams (114 per cent)

A macrocytic type of anemia was found in 34 per cent of the cases and a normocytic variety was present in 37 per cent It can be said therefore that in over two thirds of the cases the anemia is either macrocytic or normocytic in type Simple microcytic anemia was present in 16 per cent and hypochromic anemia in 13 per cent

The mean corpuscular volume averaged 93 cubic microns for the entire group with values ranging from 68 to 134 cubic microns The mean corpuscular hemoglobin concentration averaged 33 per cent but varied from 18 to 48 per cent Examination of stained smears from individuals with anemia revealed slight anisocytosis and poikilocytosis nucleated red cells were observed in these patients The platelets appeared to be present in normal numbers

The white blood cell count ranged between 2150 and 11 825 per cubic millimeter with an average count of 5987 per cubic millimeter In 35 per cent of the cases a leukopenia was present as shown by a white blood cell count below 5000 per cubic millimeter In only 4 per cent was the leukocyte count over 10 000 and it was never above 12 000 per cubic millimeter

The differential white blood cell count in the 100 patients studied by Molina and Gonzales (217) showed a degenerative change with a shift toward the left The figures were as follows the mean for the juvenile neutrophils was 1 83 per cent with fluctuations between zero and 9 per cent for the staff forms the mean percentage was 12 16 with figures ranging from 2 to 31 per cent The segmented neutrophils presented a mean of 35 84 per cent with fluctuations of 20 to 60 per cent The mean of the eosinophils was 10 2 per cent with variations from 1 to 29 5 per cent Eosinophilia was not considered significant however because of the possibility of intestinal helminth infestations in these patients The basophils varied from 0 to 1 per cent The lymphocytes were present in a mean percentage of 34 4 the lowest 16 per cent and highest 60 5

per cent The mean percentage of monocytes was 5 38 per cent with fluctuations from 1 to 16 per cent

It is possible that during the earlier stages of infection the red blood cell count and hemoglobin percentage may fall to lower levels than is indicated by the study of Molina and Gonzales (*217*) In my own experience in following patients who had received therapeutic inoculations of malaria parasites for general paresis it was not unusual to observe the red blood cell count to fall to 2 5 or 3 0 millions per cubic millimeter with hemoglobin readings between 50 and 60 per cent within a period of two or three weeks It is possible in the cases studied in Puerto Rico that many of the group may have acquired a certain amount of immunity to the condition having lived in this community since childhood and been subjected to many attacks of the disease Another explanation of the surprising mildness of the anemia was that the group studied had an unusually good diet which was higher in protein than the average Puerto Rican peasant receives

It should be kept in mind that in areas where malaria is prevalent infestation with intestinal parasites is not uncommon and hence may account for the extent and nature of the anemia when present Furthermore pregnancy should be considered as a contributing cause as well as certain diseases such as pulmonary tuberculosis sprue and dysentery

Treatment of the Anemia of Malaria —In patients with malaria in whom the anemia is of the normocytic and normochromic type no other treatment is required than the therapy directed toward the control of the malaria If the anemia is of the hypochromic or microcytic variety some complication however should be suspected and looked for and the advisability of administering iron be strongly considered

If the anemia is macrocytic in type the possibility of a complicating nutritional anemia must be considered This is especially true in natives of tropical countries where these types of anemias are relatively common It is likely that such anemias will respond to folic acid 10 milligrams by mouth daily or to liver extract intramuscularly

Blackwater Fever —This condition is an acute hemolytic anemia which occurs in association with malarial infections although its relation to the parasites of this disease is not entirely clear The symptoms develop abruptly and consist of chills fever prostration restlessness and vomiting With this there is hemoglobinuria and a rapidly developing acute hemolytic anemia followed by definite jaundice The condition is thought to be associated with malarial infections due to Plasmodium falciparum but it is not always possible to find these organisms in the blood stream and it may appear occasionally after an attack of vivax or quartan malaria Furthermore patients who have a heavy infection with plasmodium falciparum do not always have the syndrome of blackwater fever Also the administration of quinine may initiate the symptoms of the condition

It has been suggested by Fernan Nunez (227) that blackwater fever may arise as the result of a previous sensitization by the same organism Hence when a new infection develops or when allergins are liberated from the parasite by treatment with quinine or other malarial therapy an allergic response with the manifestations of a hemolytic crisis develops

The condition is always a grave complication of malaria although it has all degrees of intensity The death rate is about 50 per cent The treatment consists in the application of the usual measures for shock repeated small blood transfusions alkalinization of the urine and the discontinuance of all anti malarial therapy until the patient is convalescent

Bartonellosis

Synonyms —Carrion s disease Oroya fever verruga peruviana

Definition —This is a disease caused by Bartonella bacilliformis and transmitted by sandflies of the genus Phlebotomus The disorder is limited geographically to the vicinity of the Andrean regions in Peru Columbia and Ecuador It is characterized by four stages (1) the incubative (2) the invasive (3) pre eruptive and (4) eruptive Excellent reviews of our current knowledge of the condition and the blood changes which are observed in it are given by Ricketts (228 229)

Symptoms and Signs —After an incubation period varying from 19 to 100 days the *invasive* stage begins in which fever and anemia are present in some cases When fever and anemia are present due to this organism the condition is designated as *Oroya fever* This stage of a febrile hemolytic anemia is the period when the bartonella organisms are parasitizing the red blood cells The anemia is not a constant finding but there are no figures available to indicate how frequently it occurs during the invasive stage The *pre eruptive stage* is characterized usually by the lack of fever unless some complication as phlebitis pleuritis or encephalitis causes it by generalized aches and pains in the bones and muscles and paraesthesias especially of the extremities During this stage the blood tends to become entirely normal The *eruptive stage* is characterized by the appearance of the red cutaneous nodules the verrugas which constitute the external pathognomonic sign of the condition

For a detailed description of the clinical characteristics and the course of the disease reference should be made to the articles of Ricketts previously mentioned (228 229)

Bartonella Bacilliformis Anemia (Oroya fever) as previously stated is a febrile hemolytic anemia at which time the bartonellae are establishing themselves on the erythrocytes as parasites It is an infrequent phase of the invasive stage of Carrion s disease but the exact incidence is unknown The anemia is acute and develops so rapidly that it has been compared to the anemia of acute hemorrhage The physical findings are

per cent The mean percentage of monocytes was 5 38 per cent with fluctuations from 1 to 16 per cent

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received extensive burns and 491 people lost their lives it was observed that of the 39 living patients admitted to the Massachusetts General Hospital nine developed hemoglobinuria In one this may have been due to the sulfadiazine which was administered but in the other eight it was thought that the burns were responsible for it Five of the eight had massive hemoglobinuria the urine was grossly dark brown to almost black No information is given concerning the red blood cell count or hemoglobin estimations in these patients Hemolysis was observed in one patient who was extensively and deeply burned with large areas of charred skin which resulted in her death on the second day

Cope and Rhinelander (230) state that the cause of such hemolysis is not clear but that it may possibly be due to the actual heating of the blood present in the tissues at the time of the burn They state that in the experimental laboratory we have learned to associate hemolysis with the severity of the burn In their experience hemolysis is not encountered in dogs with hot water burns of the extremities when the temperature of the water is less than 100 degrees C or when at 100 degrees C it is applied for 15 seconds or less At 100 degrees C it appears if the burn is for 20 seconds and invariably if the burn is 30 seconds or longer It appears to be demonstrated therefore from the work of these investigators that the hemolysis may be due in part at least to the actual heating of the blood in the burned part

More recently information concerning the effect of thermal burns on the red blood cells has been made available by the studies of Shen and Ham (231) These observers studied the effects of combined second and third degree burns involving 15 to 65 per cent of the body in 40 victims of the Coconut Grove disaster in Boston In nine of these patients there was gross hemoglobinuria and in two it was minimal The maximal excretion of hemoglobin was during the first 12 to 24 hours it then rapidly decreased No significant anemia developed in the first 24 to 48 hours . Studies on normal blood showed that when it was heated to 51 to 65 degrees C changes occurred in the red blood cells consisting of fragmentation and the formation of spherocytes and microspherocytes with a striking increase in osmotic fragility and hemolysis of the erythrocytes They conclude therefore that the increased osmotic fragility apparently results from the conversion of the normal biconcave erythrocytes to more nearly spherical forms by the process of progressive fragmentation It is their belief that in thermal burns a significant number of erythrocytes may be destroyed by heat probably depending on the temperature attained by the blood the duration of the heating and the volume of blood subjected to these conditions

Further studies in 1948 by Ham and his associates (232) confirm and extend these observations

It has been found by James Purnell and Evans (233) that despite multiple whole blood transfusions anemia often develops in the first

the peculiar color of the patients which is the combination of pallor with slight icterus apathy and the usual signs of anemia such as weakness tachycardia palpitation and dyspnea on exertion

Hematological Findings —There is a sharp drop in the red blood cell count which in some instances reaches 0 5 million per cubic millimeter The anemia is macrocytic and usually hypochromic In one case cited by Ricketts (229) the mean corpuscular volume was 198 cubic microns and the mean corpuscular hemoglobin concentration 29 8 per cent The hematocrit may fall to below 10 per cent The hemoglobin values may reach extremely low levels as indicated by one of Ricketts cases in which it was 1 77 grams per 100 cc Often there are many nucleated red blood cells in the peripheral blood and the reticulocyte count may be as high as 50 per cent The leukocyte count is variable as it may be increased normal or decreased Marked leukocytosis without complicating infection is rare There may be thrombopenia with the development of *hemorrhages and petechiae*

The pathognomonic finding in the disease is the presence of the bartonella bacilliformis organisms in the erythrocyte there may be as many as 20 bacilliform bodies on each erythrocyte They appear as red violet rods with Giemsa stains measuring from 1 to 3 microns in length and from 0 25 to 0 5 micron in width They are also well stained by any of the modifications of the Romanowski methods It is the present view that the parasites are not situated within the erythrocytes but are superimposed upon them

Prognosis and Treatment —The outlook in bartonella bacilliformis anemia is extremely grave In Ricketts 30 cases (229) 22 succumbed a mortality of 73 per cent Death apparently results from a lowering of the resistance of the host with an invasion of organisms from the gastro intestinal tract and a resultant overwhelming infection Treatment in this condition is entirely smyptomatic as there are no specific forms of therapy Although there has been some question concerning the advisability of blood transfusions it is the opinion of Ricketts that they are indicated and may be life saving The other main therapeutic agent is some form of antibiotic therapy to combat the intercurrent infection which is the usual cause of death

Bartonella Disease in Animals —In rats dogs and guinea pigs infections with B muris and B canis cause anemia of a hemolytic type *This* rarely occurs however unless the spleen is removed in these animals or a deficient diet is fed

Hemolytic Anemia Due to Burns

It is known that extensive burns may be associated with a severe hemolytic anemia and in some cases a hemoglobinuria In the Coconut Grove disaster of Boston in November of 1942 in which many persons

when the amount present in the circulating plasma exceeds the renal threshold for hemoglobin

It should be carefully differentiated from hematuria Hemoglobinuria is a term which indicates that an excessive hemolysis of blood has occurred intravascularly and hemoglobin has been excreted in the urine Hematuria on the other hand is a sign that abnormal bleeding has occurred in the kidney or somewhere in the urinary tract and is characterized by the presence of intact red blood cells in the urine

Urine containing hemoglobin varies in color depending upon the concentration of the pigment which in turn is proportional to the speed at which the red blood cell destruction occurs In some hemoglobinurias such as blackwater fever the red blood cells are destroyed in great numbers over a short interval and a large amount of pigment becomes concentrated in the urine In such a condition the urine appears black but when viewed through a strong light or diluted it will be seen that the color is still reddish The presence of a relatively small amount of hemoglobin in the urine imparts a light red color which resembles the tint of claret wine the intensity of the color being proportional to the amount of pigment which is present

The Mechanism of Hemoglobinuria —The cause of hemoglobinuria is an excessive intravascular destruction of red blood cells which produce an increased amount of free hemoglobin in the circulating blood plasma When this exceeds the threshold of the kidney for hemoglobin it is excreted in the urine to which it imparts the characteristic color There are therefore two processes involved namely 1 the increased destruction of red blood cells and 2 the presence of free hemoglobin in the blood plasma which exceeds the threshold of the kidney for the pigment

The cause of excessive destruction of erythrocytes need not be discussed in detail here as it is considered elsewhere (page 141) There is undoubtedly a wide variation in the mechanism whereby red blood cells are hemolyzed It is recognized that the hemolytic process may result from the action of certain chemical agents isoagglutinins autohemolysins various parasites such as the malarial organism and that causing Oroya fever and as a result of changes in shape of the erythrocytes rendering them more fragile

The role played by the spleen is not fully understood at present but this organ is certainly vitally concerned with the destruction of blood in some manner not fully determined It is possible that its function in this respect is only a mechanical one in which it disposes of damaged red blood cells or it may be active in the actual production of hemolysins which are responsible for the increased rate of destruction of red blood cells

The renal threshold for hemoglobin is not known precisely This is indicated by the wide variation in the figures for this characteristic of

96 hours after burns During the protracted convalescence which is associated even with a small burn a moderate anemia inevitably appears Such an anemia may be exceptionally refractory to blood transfusions They conclude that hemolysis as determined by fecal urobilinogen excretion as compared to total circulating hemoglobin occurs in burns of all degrees It is great in burns of more than 20 per cent

Another possibility is that anemia may result from increased hemolysis due to contact with hemolytic gases which are inhaled (*234*) It is recognized that in cases of chronic carbon monoxide poisoning high degress of anemia may be encountered but as it is known that pure carbon monoxide is without harmful effects on the red blood cells it is assumed that the changes in the erythrocytes are caused by additional substances contained in illuminating gas (*234*) It has been demonstrated by Mayers Rivkin and Krasnow (*235*) that when red blood cells are exposed to illuminating and automobile exhaust gas, there is an increased fragility of these cells when they are brought into contact with dilute solutions of sodium chloride Drinker (*234*) states that the effect thus produced was not pronounced and must have been due to substances other than carbon monoxide since pure specimens of this gas lack such an effect There is a possibility that this anemia may be of a hemolytic nature but clearly the problem needs additional study Not only is an anemia uncommon in persons exposed to these hazards but in some there is an actual polycythemia In 1910 Karasek and Apfelback as reported by Karasek (*236*) observed that in mill workers who were almost constantly exposed to small amounts of carbon monoxide from blast furnaces the red blood cells count in two thirds was over 6 0 millions per cubic millimeter with hemoglobin values between 95 and 125 per cent

It is of interest to note that subacute or chronic hemorrhage may in part also account for the anemia associated with extensive burns It is stated by Cope and Rhinelander (*230*) that intestinal hemorrhage and ulceration are common sequels to burns and other forms of shock The origin of the lesion responsible for the bleeding is not clear but these investigators suggest that it may be due to anoxia of the mucosal surfaces arising from capillary stasis This stasis might be accounted for on the basis of hemoconcentration with increased viscosity of the blood or to diminished blood flow following arteriolar constriction

Hemoglobinuria

Definition —This condition may be defined as that state characterized by the presence of free hemoglobin but the absence of red blood cells in the urine Such a finding is always indicative of an excessive intravascular destruction of red blood cells which exceeds the capacity of the reticulo endothelial system to convert the abnormal amount of hemoglobin thus liberated into bilirubin Hence it is excreted in the urine

urine it is an indication that the hemolytic process is acting with great rapidity and intensity The same cause when operating more slowly and mildly will produce the various types of acute subacute or chronic hemolytic anemia The etiology of this group therefore need not be discussed here The paroxysmal hemoglobinurias however are of such a nature as indicated by the intermittency of the hemoglobinuria that they should be placed in a separate division The paroxysmal hemoglobinurias may be classified as follows

I Paroxysmal Cold Hemoglobinuria (Syphilitic)
II Paroxysmal Cold Hemoglobinuria (Non syphilitic)
III Paroxysmal Nocturnal Hemoglobinuria
IV March (Exertional) Hemoglobinuria

Paroxysmal Cold Hemoglobinuria (Syphilitic) —Although this is a rare condition it is probably the most important of all types of the paroxysmal hemoglobinurias for it is the most frequently encountered variety which is associated with important symptoms The first case of this type was described by Dressler in 1854 (239) and since that time about 350 cases have been published (*240*)

A typical attack is precipitated by exposure to cold or in some instances simply by immersing the hands in cold water for 10 to 20 minutes as demonstrated by Rosenbach in 1880 (*241*) In 1904 it was observed by Donath and Landsteiner (*242*) that such an individual s red blood cells could be sensitized by cold so that when they were subsequently warmed hemolysis resulted

Cold hemoglobinuria may be defined as a condition characterized by the transient appearance of hemoglobinuria associated with exposure to cold which apparently causes an autohemolysin in the blood to unite with the erythrocytes It is of interest to note that *almost all of these patients have clinical evidences of syphilis* either acquired or congenital

The first patient with this condition seen by the author was in 1917 in Boston The patient complained of attacks characterized by a chill with a subsequent febrile rise headache generalized body aches and pains and the appearance of a reddish black urine Her Wassermann reaction was positive and it was known that her husband was suffering from general paresis The attacks could be induced by the *Rosenbach test* which consists of placing the hands or feet in cold water for 10 to 15 minutes and the *Landsteiner Donath reaction* was positive This phenomenon is determined by separating the patient s serum and cells and preparing a 5 to 10 per cent suspension of red blood cells in saline Equal parts of the patient s serum and fresh guinea pig complement are added to the suspension of erythrocytes and this is chilled for 30 minutes Apparently the chilling permits the absorption of the lysin by the red

the kidney which are given by different investigators For example Ottenberg and Fox (*151*) reported that in a group of normal subjects, the hemoglobin appeared in the urine when the plasma level reached 96 milligrams per 100 cc of blood but that it might be absent in the urine of other normal subjects when the level rose to as high as 288 milligrams per cent It is concluded by Hoffman and Kracke (*237*) that the renal threshold is usually between 130 to 150 milligrams per cent

There are two views concerning mechanism of the passage of the hemoglobin molecule through the kidney One is that it does not pass through the glomular membrane until a certain plasma concentration is reached and it is at this level that the hemoglobin appears in the urine With a fall below this critical level the hemoglobin no longer passes through the kidney and the hemoglobinuria disappears In the opinion of Bogniard and Whipple (*238*) it is assumed that the hemoglobin passes through the glomular filter and normally is reabsorbed by the tubular epithelium According to this view hemoglobin appears in the urine when the rate of filtration exceeds that of reabsorption The exact mechanism which permits hemoglobin with its molecular weight of 67 800 to pass through the glomerulus is not known

The Pathologic Lesion in the Kidneys Due to Hemoglobinuria —This is confined to the renal parenchyma and the characteristic findings are as follows according to Hoffman and Kracke (*237*) In severe cases with anuria and death hematin crystals are frequently found mechanically blocking the tubules There is necrosis and fragmentation of the convoluted tubular epithelium and extensive interstitial edema As this type of epithelium has remarkable regenerative capacity and provided it is not too extensively damaged it may return to normal

In 1925 Baker and Dodds (*152*) showed that hemoglobin could be excreted by the kidney without harm if the pH of the urine was 6 0 or higher but below 6 0 the hemoglobin was precipitated in the tubules DeGowin and his associates (*153*) reported that hemoglobin could be transfused into dogs and found that much larger quantities of hemoglobin could be eliminated by the kidneys when the urine was kept alkaline whereas if the urine was acid the animals died of uraemia More recently however DeNavasquez (*154*) has reported that in rabbits the excretion rate of hemoglobin through the kidneys was higher in animals with an acid urine than in those in which it was alkaline He also states that he had observed cases with transfusion fatalities in which an alkaline urine did not prevent anuria and death with uremia

Classification of the Hemoglobinurias —The grouping of these conditions into the two principal types of hemoglobinuria and the paroxysmal hemoglobinurias is obvious and serves a useful purpose It should be emphasized that the first group is composed of the same subgroups as those of the hemolytic anemias The causes of the two conditions are the same with the exception that when free hemoglobin is present in the

antibodies as well as autoantibodies and therefore will clump all red blood cells including group O They suggest that such blood may be typed by performing the test at body temperature and transfusion reactions may be prevented by placing hot water bottles around the container holding the blood to be transfused

CHRONIC HEMOLYTIC ANEMIA WITH PAROXYSMAL NOCTURNAL HEMOGLOBINURIA

(Marchiafava Micheli Syndrome)

Definition —This is a rare type of hemolytic anemia characterized by the symptoms and signs of chronic red blood cell destruction associated with attacks of hemoglobinuria which occur chiefly at night It was first described by Marchiafava and Nazari in 1911 (*247*) and more completely by Micheli in 1931 (*248*)

Reviews dealing with the clinical features of the disease have been written by Hamburger and Bernstein (*249*) Witts (*250*) Dacie Israels and Wilkinson (*251*) and Marks (*252*) The pathological findings have been described by Scott Robb Smith and Scowen (*253*)

Etiology —Almost three fourths of the cases are males and the age of greatest incidence is between 20 and 40 years the oldest case being 40 years and the youngest 15 years The condition is not common as less than 50 cases have been reported in the literature

The syndrome is characterized by a continuous intravascular hemolysis and hemoglobinemia with an intensification of the process during sleep which results in the appearance of hemoglobin in the urine The belief that the essential lesion of the disease is inherent in the erythrocytes of the individuals affected is supported by the work of Ham (*254*) Ham and Dingle (*255*) Dacie Israels and Wilkinson (*251*) Hickey and Malley (*256*) In 1949 Dacie and Mollison (*257*) studied the survival rate of erythrocytes taken from a patient with nocturnal hemoglobinuria when transfused into an adult and an infant In both recipients the red blood cells were eliminated more rapidly than normal In the adult the elimination of the transfused erythrocytes was rapid as indicated by a disappearance of 50 per cent of the cells in five days by the 10th day only 30 per cent were left elimination of the remaining red blood cells was slow as 20 per cent still survived a further 20 days In the infant recipient the elimination was more rapid than normal but less so than in the adult In both however the transfused abnormal cells disappeared more rapidly than the normal rate of elimination which averaged about 1 per cent per day

Ham (*254*) after a comprehensive study of five cases has concluded that the fundamental abnormality resides in the red blood cells He observed that nocturnal hemoglobinuria was associated with sleep and

blood cells. Following this, the mixture is incubated at a temperature of 37 degrees C for 30 minutes which results in the hemolysis of the patient's red blood cells. Furthermore the red blood cells of a normal person can be substituted in the reaction and the serum from the patient with cold paroxysmal hemoglobinuria will produce the same hemolysis under the conditions outlined. This demonstrates that the condition is not an abnormality of the erythrocytes but that the lysin must be in the patient's serum.

During the attack the red blood cells may fall precipitously to 2.5 or 3.0 millions per cubic millimeter or even lower. With this as is to be expected a mild icterus with a positive indirect van den Bergh may be present as is also a reticulocytosis.

The only therapeutic measures which are of value are the prevention of exposure to cold and the treatment of the syphilitic condition which is almost invariably present. Untreated cases may continue with exacerbations of hemolysis for years. With antisyphilitic therapy the auto*hemolysin may disappear from the blood and the serologic reactions for* syphilis become negative.

Paroxysmal Cold Nonsyphilitic Hemoglobinuria.—In more recent years it has been demonstrated that in certain infections, especially *primary atypical pneumonia, certain antibodies designated "cold agglutinins"* are present in the patient's blood. These have the ability to produce clumping of the patient's cell at ice box temperatures. Erythrocytes thus clumped are more susceptible to hemolysis than normal cells as a result of slight trauma. In vivo the cold agglutinins also cause clumping and hemolysis of the red blood cells in the blood stream. This disintegration of the erythrocytes usually occurs when the patient is exposed to cold but apparently when the agglutination titre is high it may be produced at room temperature. In some instances agglutination titers have been reported as high as 1:2,000,000 *(243)*.

The two types of paroxysmal hemoglobinuria were first differentiated by Stats and Wasserman *(244)*. Later Stats *(245)* produced evidence to indicate that hemolysis of the patient's erythrocytes in the nonsyphilitic type *was due to their increased susceptibility to mechanical trauma* and was not concerned with the Donath-Landsteiner type of hemolytic reaction. A case of this type is reported by Malley and Hickey *(240)* who demonstrated the presence of a high titre cold agglutinins in the patient's blood and an increased susceptibility of the red blood cells to mechanical trauma. It is their opinion, however, that the precise mechanism which causes hemolysis in this syndrome is not established.

It is pointed out by Estren and Dameshek *(246)* that in such patients the hemolysis may be extensive and result in a severe anemia. They also emphasize that it may be difficult to group and cross match blood for transfusion in these patients for transfusion as cold agglutinins are iso

uria may be absent for a period of several months. A moderate albuminuria may be present

Prognosis and Treatment.—There is no satisfactory treatment for this condition. Although the administration of alkaline salts may decrease the amount of hemolysis for brief intervals there may be an increased amount of red blood cell destruction following the cessation of such therapy or even while it is being given. Splenectomy reported in two cases by Ham (*254*) was ineffective. Blood transfusions are often associated with hemolytic reactions of varying severity but in some instances this may be followed by periods of ranging from several days to weeks during which time the rate of hemolysis is significantly decreased. At such times the hemoglobin content and red blood cell count of the peripheral blood is often significantly increased. Transfusions although they may produce benefit should be given cautiously on account of the possible harmful immediate reactions. The only known beneficial therapeutic measures are a well balanced adequate diet, a limitation of activity and the avoidance of infection. Iron may be given orally but it is unlikely that this will be of benefit. In the five attacks of hemoglobinuria observed in a patient by Hickey and Malley (*256*) over a period of 5 years four of these followed iron therapy and one occurred after a blood transfusion. A causal relationship however is by no means established by these observations as other patients have not reacted in a similar way to these therapeutic agents. As previously emphasized blood transfusion should be given cautiously.

There is no proof that large doses of liver administered over a long period of time is of benefit.

March Hemoglobinuria

Definition.—The name *march hemoglobinuria* is based on the observation that a benign hemoglobinuria is sometimes observed in soldiers or other young males following prolonged marches or other strenuous exertion. The condition tends to disappear spontaneously after several months without producing significant symptoms or sequelae.

It was first observed by Fleischer (*258*) in 1881 in a young soldier who had hemoglobin in the urine after a long march. The literature dealing with this subject is reviewed by Gilligan and Blumgart (*259*), Hobbs (*260*) and by Lubran and Sakula (*261*).

Etiology.—According to Gilligan and Blumgart (*259*) up to 1941 there had been only 40 cases reported, mainly in the German literature. The fact however that these authors observed three cases in a relatively short time and subsequently also several other examples of the condition in otherwise normal athletes after strenuous exercise suggests that the incidence of the condition is greater than has been previously supposed. With the large number of young men who are now in military training

not with the patient's posture with ingestion of food or fluid or with the time of day or night during which sleep occurred. This investigator suggested that the greater hemoglobinemia and hemoglobinuria during sleep are induced by an excessive intravascular hemolysis associated with an increased acidity of the blood especially of regions of the body subject to stasis such as the spleen. Ham (254) also noticed that in vivo free hemoglobin was present at all times in the plasma which he interpreted as an indication of continuous intravascular hemolysis. Increased acidity produced by the ingestion of acid forming salts was associated with a transient increased in hemoglobinemia and hemoglobinuria in some cases. Alkalosis due to the ingestion of alkaline salts and by hyperventilation was associated with a transient decrease in the hemoglobinemia and hemoglobinuria.

It is the opinion of Estren and Dameshek (246) however that despite numerous studies the exact cause of the condition remains obscure. They state that the changes in the pH of the blood during sleep, although in the direction of acidity are so small that it probably bears no relationship to the destruction of red blood cells in vivo. According to Estren and Dameshek (246) there is no convincing evidence that posture affects the hemolysis. They state that in some cases perhaps hemolysis may be prevented by sleep in the erect position but in others this result is not observed.

Symptoms and Signs.—The symptoms are those of a chronic hemolytic anemia associated with a transient hemoglobinuria characterized by the passage of red urine during sleep. Vague abdominal cramps backache malaise, and a dull headache are commonly present in these patients. These compaints are most frequently present following sleep. Exacerbations may be associated with any type of infection such as that involving the upper respiratory passages. Since the anemia may be severe as indicated by a red blood cell count of 1.5 millions per cubic millimeter the symptoms common to all anemias such as ease of fatigue, weakness pallor dyspnea and palpitation may be pronounced. The physical signs are evidence of pallor with a mild icterus and sometimes a barely palpable liver and spleen.

Changes in the Blood.—There is a moderate to severe normochromic normocytic or microcytic anemia with a leukopenia and a reticulocytosis. In Ham's cases (254) the mean corpuscular volume varied from 69 to 131 cubic microns and the mean corpuscular hemoglobin concentration from 29 to 31 per cent. The white blood cells fluctuated between 3330 to 6000 per cubic millimeter with a normal differential and platelet count. There is no increased fragility of the erythrocytes to hypotonic salt solutions in this condition. The blood bilirubin is usually moderately elevated but it may be between 0.8 and 3.6 milligrams per cent.

The urine contains the greatest amount of hemoglobin following sleep but it is often present at other times. In some patients the hemoglobin

the urine is positive and there are no red blood cells present then the pigmentation must be due to either free hemoglobin or myohemoglobin

The diagnosis of hemoglobinuria may be confirmed by spectroscopic examination which shows the presence of oxyhemoglobin in the urine It should be kept in mind that there are two conditions which may lead to hemoglobinuria in the absence of hemoglobinemia namely acute nephritis and infarction of the kidney The condition may be differentiated from paroxysmal hemoglobinuria of the chill or syphilitic type by means of the Landsteiner Donath reaction (page 213) and the Rosenbach test and from paroxysmal nocturnal hemoglobinuria by the clinical features and the diagnostic acid hemolysis test of Ham (254)

Prognosis —The condition is ordinarily regarded as benign but it is important because it may be confused with some other more serious type of paroxysmal hemoglobinuria or with hematuria The case of an athlete is reported by Fisher and Bernstein (262) who continued to exercise strenuously without ill effects as fever or constitutional reactions It appears to be good judgment however for a person in whom this phenomenon occurs to refrain from strenuous exertion

It is reported by Lubran and Sakula (*261*) that previous observers have administered ascorbic acid to such patients with variable results They gave this drug to three patients and noted a rapid and dramatic cessation of hemoglobinuria following large doses of this preparation They conclude however that additional studies are necessary before the value of ascorbic acid therapy can be determined

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under circumstances which provide close medical observation it is possible that an increased number of cases will be detected

The fact that this condition is not commonly considered by many physicians may lead to the failure of its recognition and confusion of such a benign state with other more serious causes of hemoglobinuria or hematuria Studies by Blumgart and Gilligan (259) indicate that hemoglobinemia sometimes accompanied by hemoglobinuria appears in a large proportion of cross country and marathon runners Furthermore it may occur following short walks or runs in some individuals on account of postural or mechanical factors

The cause of this condition is related definitely to physical exertion It has been demonstrated also that it may be precipitated with less exertion when a certain posture is assumed during exercise For example it was observed in one individual (259) whose attacks could be reproduced readily by 30 minute walks If the same or even greater amounts of exercise was accomplished in a moderately kyphotic position either during walking or riding a bicycle no hemolysis occurred Furthermore hemoglobinemia or hemoglobinuria are not produced by standing still in the erect position for a prolonged period of time by lying in a lordotic position or by hyperventilation It is not possible to cause local hemoglobinemia with exercise of the hand when venous stasis is produced by means of a tourniquet on the arm It is estimated that only from 6 to 40 cc of blood is destroyed intravascularly during an attack and that less than 10 per cent of the hemoglobin thus freed in the plasma appears in the urine

Symptoms and Signs —Ordinarily there are no symptoms or signs of the disease and the condition is mainly of importance because the red color of the urine may be misinterpreted as being indicative of a more serious condition It has been said that weakness and pain in the lumbar region and muscles sometimes accompanies the hemoglobinuric episodes It has been reported (259) that chronic icterus may be present and there may also be a palpable liver and spleen but these findings are unusual It is uncommon for any of the cases to show anemia reticulocytosis increased platelet counts or abnormal fragility tests although one of the patients reported by Lubran and Sakula (261) had a red blood cell count of 3 2 millions per cubic millimeter and a hemoglobin of 8 4 grams per 100 cc Tests for isohemolysins and autoagglutinins are negative The hematocrit and red blood cell counts are normal at all times and the Rosenbach test and the Donath Landsteiner reaction are negative

Examination of the Urine —The urine in this condition is pink red or black depending on the amount of hemoglobin present Such coloration must be differentiated from hematuria porphyrinuria in which the color is due to urofuscin myoglobinuria and from the red color due to beets phenolphthalein or neoprontosil If the benzidine or guaiac test on

the urine is positive and there are no red blood cells present then the pigmentation must be due to either free hemoglobin or myohemoglobin

The diagnosis of hemoglobinuria may be confirmed by spectroscopic examination which shows the presence of oxyhemoglobin in the urine It should be kept in mind that there are two conditions which may lead to hemoglobinuria in the absence of hemoglobinemia namely acute nephritis and infarction of the kidney The condition may be differentiated from paroxysmal hemoglobinuria of the chill or syphilitic type by means of the Landsteiner Donath reaction (page 213) and the Rosenbach test and from paroxysmal nocturnal hemoglobinuria by the clinical features and the diagnostic acid hemolysis test of Ham (*254*)

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CHAPTER VI

PERNICIOUS ANEMIA AND OTHER MACROCYTIC ANEMIAS

Synonyms.—Addisonian anemia. Biermer's anemia. Primary anemia.

Definition.—Pernicious anemia is a chronic disease affecting both sexes equally, most commonly occurring in the white race in temperate climates at middle life or later, characterized by a macrocytic normochromic anemia with a megaloblastic bone marrow, a persistent histamine resistant achlorhydria, frequently by degenerative changes in the peripheral nerves and spinal cord, and often by a recurrent glossitis. The anemia is thought to be due to a failure of the gastric glands to secrete the enzyme-like *intrinsic factor of Castle in normal amounts which* results in an abnormal maturation of the red blood cells in the bone marrow. There is a prompt response to antipernicious anemia medication but untreated cases progress slowly, usually with remissions, to a fatal termination.

The History of Pernicious Anemia.—The earliest description of pernicious anemia is generally credited to Thomas Addison by English speaking people of the world and reference is made to his remarks concerning the disease in the introduction of his last and best known monograph *On the Constitutional and Local Effects of Disease of the Suprarenal Capsuls* published in 1855 (*1*). It was, he says, whilst seeking to throw some additional light upon this form of anemia that he discovered a completely different syndrome, namely, Addison's disease or adrenal insufficiency.

There are several things to be noted, however, about this description. Attention had been directed toward it six years before, in 1849, when on March 15 of that year Addison read a paper before the south London Medical Society on "Anemia—Disease of the Suprarenal Capsuls," which was published in the *London Medical Gazette* for March 1849 (*2*). But in this publication there was no clear differentiation between pernicious anemia and adrenal insufficiency. In regard to Addison's original and brief publication in 1849 Pye-Smith (*3*) says that "this shows, however, truth in the making, for the author had not yet clearly separated what we now call idiopathic anemia for what we call morbus addisonii (namely adrenal insufficiency)." According to Stephen MacKenzie (*4*) this astute observer had spoken in his clinics concerning idiopathic anemia several years prior to the appearance of this publication.

Addison's contribution in 1855 dealing with idiopathic anemia [redacted] made up of a few brief paragraphs and [redacted] found in the preface to his classical description on the now well known disease of the adrenal glands which bears his name In these paragraphs he did apply the term idiopathic to the anemia and stated that the condition arose from no discoverable cause whatever Furthermore he recognized that the malady was almost always fatal that the onset was insidious that the usual symptoms of anemia were present that there was often [redacted] preservation of the patient's body fat that therapy was ineffective and that some form of fatty degeneration might have a share at least in its production

While undoubtedly Addison deserves credit for the recognition of the syndrome it [redacted] known now that similar cases had been recognized previously the most frequently cited one being the case observed in 1822 by the Scottish physician James Scarth Combe He reported his observations to the Medico Chirurgical Society of Edinburough on May 1 1822 and it appeared in the transactions of the society in 1824 (5) with [redacted] full clinical account and a postmortem description Moreover as pointed out by Long (6) reference to this case was made in the well known *Principles and Practice of Medicine* by John Elliotson in 1839 a work with which all English physicians including Addison were probably familiar

From Combe's description it is quite apparent that his patient had a severe anemia which in the course of about six months proved fatal It is certain that the symptoms were those of anemia but there is nothing to indicate definitely that the patient had true pernicious anemia In fact there is some evidence in the publication which suggests strongly that it was some other type of anemia from which the patient was suffering perhaps of the aplastic type or that due to subleukemic leukemia or a severe nephritis It is stated for example that the patient had a deadly pale color and no reference [redacted] made to the well known yellowish tint characteristic of pernicious anemia It is also recorded that the patient's tongue [redacted] covered with a dry fur which rarely if ever occurs in patients with pernicious anemia as we see it today Although Combe should be given the credit for having described [redacted] severe case of anemia of unknown etiology which terminated fatally there [redacted] no absolute proof that the patient was suffering from pernicious anemia and some rather convincing evidence that he was not

While Addison's account was undoubtedly based on observations of patients some of whom had what we now call true pernicious anemia it should be noted that he failed to record or observe for one reason or another some of the most outstanding diagnostic features of the condition For example no mention is made of the yellowish tint to the skin and conjunctivae or the alteration in the blood for complete blood examinations as now employed was not then known For the same reason there was no study of the gastric secretion Furthermore he apparently did not observe the dark color of the urine which [redacted] present

at intervals the hyperplastic bone marrow the degenerative changes in the spinal cord the glossitis or paraesthesia and but brief reference was made to a possible fatty degeneration of the semilunar ganglion In other words he described a fatal anemia of unknown etiology occurring usually in middle age persons who were comparatively well nourished

Apparently Addison s writings did not establish immediately the condition in England as a clinical entity for in 1874 19 years after his more complete description of pernicious anemia an editorial appeared in the *Medical Times and Gazette* on November 21 entitled Pernicious Anemia a New Disease In this it is stated that Immermann of Basel had confirmed the observations of Professor Anton Biermer of Zurich and added that the editorial writer had not been aware that any case had been reported in Great Britain This was clearly in error as emphasized in a letter published seven days later in the *British Medical Journal* for November 28 1874 in which Samuel Wilks asserted that he had heard Thomas Addison lecture on the disease as far back as 1843

It is clear to any present day hematologist that the description of Professor Anton Biermer of Zurich came nearer the mark than any other which had then appeared in describing pernicious anemia as it is now recognized Biermer s report as it appeared in the *Correspondenblatt fur Schweizerische Aertze* Jahrgang 11 1872 No I (7) is his most complete one but an earlier description had been given in the autumn of 1868 before the Dresdener Naturforscherversammlung In this it was stated that he had been investigating the peculiarities of this disease since 1867 The contributions of Biermer may be summarized as follows 1 he gave the disease the name progressive pernicious anemia 2 his efforts directed the attention of the medical profession throughout Europe to this malady and hence it was the beginning of a more widespread interest in the condition 3 he gave a good description of the symptoms of the anemia and deserves special credit for pointing out for the first time the highly important fact that the patients frequently had a yellowish white color without icterus and that often purpura and retinal hemorrhages were present and 4 he also noted that although emaciation might be present the subcutaneous fat was retained and that almost always hemic murmurs usually systolic in time may develop during the course of the disease

A fatal termination occurred in all of his cases It should be noted however that Biermer did not mention the paraesthesia of the hands and feet which are now recognized as occurring in 90 per cent of all the patients nor was reference made to recurrent glossitis which is present in 65 per cent of the patients whom we see today Furthermore he erroneously included in the group several patients who were suffering from follicular ulceration of the large intestine He also considered some cases associated with pregnancy and the puerperium to be of this

type The modern hematologist differentiates them from pernicious anemia although they may bear some resemblances At necropsy Biermer noted the widespread fatty degeneration of the heart and other organs and attributed this change to the altered composition of the blood

It is exceedingly difficult to determine from the earlier descriptions of pernicious anemia whether or not the condition which is being discussed is a true example of the disease At the present time it is commonly accepted that if a person of middle age or older has the symptoms of an anemia and a yellowish tint to the skin and conjunctivae is present there is a good chance that the disease is pernicious anemia Furthermore if there is numbness and tingling of all four extremities and the patient complains of attacks of recurrent glossitis with or without atrophy of the papillae over the dorsum of the tongue it is most likely that the patient has this type of anemia If in addition there is an achlorhydria following the injection of histamine one is almost certain that the patient has true pernicious anemia even before the blood is examined Our present day diagnostic features include the finding of a macrocytic anemia with a high mean corpuscular hemoglobin concentration and color index a leukopenia a diminution in platelets and a remarkable therapeutic response to potent antipernicious anemia therapy

When all of these manifestations of the disease are taken into account the diagnosis of pernicious anemia is highly accurate In the days of Combe Addison and Biermer however it was not possible to examine the blood with the methods which are employed today gastric analyses were not done and of course there was no effective treatment for the disease Moreover the early reports of Addison and Combe do not mention the yellowish tint which is often so conspicuous but this was described by Biermer Furthermore recurrent glossitis is not discussed nor is atrophy of the papillae of the tongue or of numbness and tingling of the hands and feet It is remarkable that these manifestations of the disease which are so prominent in the clinical picture of our patients today were either absent or overlooked by those who were responsible for its earlier descriptions Even now with all of the modern diagnostic methods it is possible to mistake the true nature of the anemia in patients with pernicious anemia If this is the case at present the possibilities of an erroneous diagnosis must have been infinitely greater when cases of severe anemia were first recognized in the days of the pioneer observers

The credit for the earliest description of true pernicious anemia is difficult to assign for the reasons just cited In England it is given to Combe (1820) and Addison (1849) But as Coupland says (8) some consideration must be given to the descriptions of the disease by Andral in 1823 Marshall Hall in 1837 Biorry in 1841 and Pearce in 1845

Doubtless also there are others who have made important contributions to the development of the knowledge of pernicious anemia whose publications have been unintentionally overlooked

Other important dates in the history of the development of our knowledge of the disease are as follows Samuel Fenwick in 1877 (9) first observed that the mucous membrane of the stomach showed a pronounced atrophy Noted first by Barclay in 1851 (*10*) the importance of recurrent glossitis was emphasized by William Hunter in 1889 (*11*) although Laache in 1883 has also previously described this complaint in these patients (*12*) According to Castle (*13*) Grawitz and others" first recognized the importance of the alterations in the gastric secretions in 1896 It is known that Martius in 1897 (*14 15*) also discussed the importance of the achlorhydria Faber and Bloch (*16*) in 1900 collected 33 cases of the disease in which a gastric analysis had been done and in all it was found that an achlorhydria or hypochlorhydria existed One of the most complete early papers dealing with the achlorhydria was that of Levine and Ladd published in 1921 (*17*) They found that an absence of free hydrochloric acid occurred in practically all of these cases Faber (*18*) in 1895 *first called attention to the association of Pernicious* Anemia with a stricture of the small intestine Among those who first emphasized the importance of the lack of hydrochloric acid in the gastric secretions despite the hematological remissions was Hurst in 1923 (*19*) He rightfully concluded that the achlorhydria was the most constant abnormality in the disease and that it persisted throughout all of its phases

Probably Laache (*12*) in 1883 first described some of the important blood changes including the high color index He was apparently the first to note the large deeply colored corpuscles (macrocytes) in the circulating blood and considered them to be the main distinctive hematological feature in this type of anemia Microcytes were first described by Eichhorst (*20*) in 1887 and poikilocytosis by Quincke (*21*) in 1876 A comprehensive discussion of the early history of pernicious anemia with an extensive bibliography and a discussion of the early descriptions of changes in the blood is given in the monograph on pernicious anemia by William Hunter (*11*)

According to Lazarus (22) the solid basis for the definition of pernicious anemia was first recognized when the important gap in our knowledge concerning the changes in the blood was filled He states that several of the blood changes peculiar to the disease were at least in part mentioned in the older observations of Hayem (1877) Eichhorst (1876) Laache (1883) and H F Muller (1877) It was the work of Paul Ehrlich (1880) however which placed the hematology of pernicious anemia on a firm basis This was in part due to the remarkable ability of this investigator to make accurate observations and also was

dependent on the improved methods of staining and studying the cells of the circulating blood and bone marrow which he introduced

The earliest observation that heredity might be of importance in the etiology was emphasized by the publication of Klein (23) in 1891 in which he reported the disease in four members of one family a sister and three brothers The literature in regard to this feature is reviewed by Stamos (24)

The relationship between pernicious anemia and Dibothriocephalus infestation was originally described by Reyher (1884) and Tuneberg (1888) The high color of the urine of patients with this disease during relapse was noted by Eichhorst (1876) Quincke (1876) Pye Smith (1883) and Bristowe (1858) As early as 1875 Pepper employed blood transfusions in treatment of this condition

In North America the disease became more widely known through the efforts of Palmer Howard Professor of Medicine at McGill University who gave a paper dealing with the condition before the International Medical Congress held in Philadelphia in 1875 (25) In the previous year William Pepper Professor of Medicine and later Provost at the University of Pennsylvania brought the attention of the physicians of this country to the condition by the publication of a paper (26) concerning it in the *American Journal of Medical Sciences* In this article is found the earliest description of the bone marrow in this disease which according to the late William H Welch (27) was based on the work done by Pepper in Julius Conheim s laboratory and which served as a basis for the monograph dealing with the same subject published by the latter author in 1876 It is of interest to note that in this same article Pepper employed blood transfusions as a form of treatment but warned against the severity of the reactions which his patients had experienced Byrom Bramwell in 1877 (28) made the original observations on arsenic as a therapeutic agent in this condition Quincke in 1877 (29) noted the pigmentary changes in the livers of patients dead of the disease Pye Smith in 1882 suggested that gray hair was more common in patients with this disease (30)

Early Observations on Changes in the Nervous System —In 1884 O Leichtenstern (*31*) reported what he thought to be the coincidental association of tabes dorsalis in two patients with pernicious anemia In this important contribution changes were described which are characteristic of alterations in the posterior columns of the spinal cord but no mention is made of sensory abnormalities such as paraesthesias It is almost certain that these patients had the pathological changes of subacute combined degeneration of the spinal cord which is now accepted as a part of the clinical picture of pernicious anemia The focal lesions in the spinal cord in this condition were first noted by Lichtheim (32) in 1887 The classical changes of subacute combined degeneration of

the spinal cord were first described in the United States by C E Riggs in 1896 (33) and again in 1913 (*34*) One of the earliest and most complete clinical and pathological descriptions of subacute combined degeneration of the spinal cord was by Russell Batten and Collier (35) in 1900 It was Albert M Barrett of the University of Michigan who in 1913 was the first or among the earliest to direct attention to the focal lesions in the brain in this condition (*36*) Carl D Camp in 1912 gave one of the earliest descriptions of the mental changes which are sometimes associated with this condition (*37*) To Hamilton and Nixon (*38*) in 1921, should be accorded the credit of emphasizing the frequency of degenerative changes in the peripheral nerves and attention to the paraesthesias which had previously lacked an established anatomical basis for their existence

The Origin of the Liver Treatment in Pernicious Anemia —The most remarkable advance in our knowledge concerning pernicious anemia came in 1926 when George R Minot and William P Murphy introduced into clinical medicine the use of liver in the treatment of the disease Their original contribution was read before the Association of American Physicians May 4 1926 and published in the transactions of that organization for the same year (*39*) Their second publication appeared a few months later in the *Journal of the American Medical Association* (*40*)

The initial public reference to the modern treatment of pernicious anemia with liver was one made by Dr George R Minot at a meeting of the Suffolk District Medical Society in Boston on April 28 1926 Dr Minot participated with other members of the Staff of the Collis P Huntington Memorial Hospital of Boston in discussing the various phases of malignant lymphoma As Minot says in a personal communication to me "toward the end of my speech I had a little something to say about pernicious anemia and in the course of not over three minutes I told them that I thought patients with pernicious anemia might be greatly benefited by feeding them liver generously There was no publication covering the remarks of the evening It is of interest to note that the initial statement before a medical society concerning what eventually proved to be a major therapeutic epoch in the management of the anemia was heard without arousing any particular enthusiasm among those present

As previously stated the first actual formal presentation of the convincing evidence that liver exerted a beneficial effect in the treatment of patients with pernicious anemia was given by Minot before the Association of American Physicians at Atlantic City on May 4 1926 This was published by George R Minot and William P Murphy (*39*) in the *Transactions of the Association* which was not distributed however until after the publication by Minot and Murphy entitled Treatment of Pernicious Anemia with a Special Diet was printed in the August 14th

1926 number of the *Journal of the American Medical Association* (40) Another similar article appeared in the *Boston Medical and Surgical Journal* in August 26 1926 (41)

In the past it had been established beyond the slightest question that pernicious anemia was invariably a fatal disease with an average duration of life not exceeding two to three years from the appearance of the initial symptoms In this respect it was just as fatal as cancer of the stomach but with the exception that occasionally patients would survive for a much longer period of years and furthermore in almost every case of pernicious anemia there was a spontaneous remission usually persisting for three to six months As Meulengracht said in 1939 (42) The introduction of liver therapy was an epoch making occurrence I might say a revolution which took place when Minot and Murphy tore down much of the veil of mystery surrounding pernicious anemia

The use of liver as a method of treating patients with anemia was brought to the attention of clinicians by the convincing experimental work of George H Whipple then Professor of Research Medicine and Director of the Hooper Foundation for Medical Research Medical School of the University of California and since 1921 Dean and Professor of Pathology at the University of Rochester As early as 1918 this investigator began studying the regeneration of hemoglobin in the circulating blood of dogs according to an original and ingenious plan which was both effective and simple He placed dogs on a known diet and then produced an anemia by the repeated removal of blood The anemia having been induced the basic diet was maintained constantly but changed at intervals by the addition of meat liver and other substances The results were recorded in terms of the number of cubic centimeters of blood which it was necessary to remove in order to hold the hemoglobin of the animals at a constantly low level His first paper dealing with this subject was published in association with C W Hooper in the *American Journal of Physiology* for March 1 1918 (43) with the title Blood Regeneration After Simple Anemia I Curve of Regeneration Influenced by Dietary Factors" The initial publication referring to the effect of liver on the regeneration of blood appeared in the *American Journal of Physiology* for September 1920 (44) with the title Blood Regeneration Following Simple Anemia IV This was written in collaboration with F S Robscheit Robbins and C W Hooper In this article it is concluded that cooked liver is able to induce blood regeneration even under the most unfavorable conditions" It was concluded that cooked liver was as efficient as meat in this respect and that it *may be even more efficient in promoting complete regeneration subsequent to a standard anemia*

The relation of Whipple s work to the use of liver on the treatment of pernicious anemia by Minot is well expressed by James H Means and

the spinal cord were first described in the United States by C E Riggs in 1896 (33), and again in 1913 (34) One of the earliest and most complete clinical and pathological descriptions of subacute combined degeneration of the spinal cord was by Russell, Batten and Collier (35) in 1900 It was Albert M Barrett of the University of Michigan who in 1913 was the first or among the earliest to direct attention to the focal lesions in the brain in this condition (36) Carl D Camp in 1912 gave one of the earliest descriptions of the mental changes which are sometimes associated with this condition (37) To Hamilton and Nixon (38) in 1921 should be accorded the credit of emphasizing the frequency of degenerative changes in the peripheral nerves, and attention to the paraesthesias which had previously lacked an established anatomical basis for their existence

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however had it been recognized that liver possessed the remarkable curative effects on the anemia of pernicious anemia until this was demonstrated by Minot and Murphy Felon in 1921 (47) and Gibson and Howard, in 1923 (48) basing their work on the experimental findings of Whipple and Robscheit Robbins fed a high iron high vitamin diet which contained a certain amount of liver The latter concluded that the use of diets in anemia is urged but they "did not feel that established therapeutic measures to promote hematogenesis should be neglected"

It was indeed fortunate that Minot used liver in treating patients with pernicious anemia as well as those with the anemia of chronic hemorrhage From Whipple's work it appeared logical that liver would be effective in the anemia of chronic hemorrhage but there was no convincing evidence that it could accomplish good in true pernicious anemia Then the almost unbelievable occurred! Although possibly the patients with the so-called "secondary anemia" did show some slow improvement the most prompt dramatic and decisive change occurred in the patients with pernicious anemia Within a few days the blood began to improve the appetite became keener the fever and gastro-intestinal symptoms disappeared their strength returned and within a short time they were up and about

Of great assistance in determining the effect of the liver therapy was the feature introduced by Minot of enumerating the reticulocyte count in the circulating blood as an index of the activity of the red blood cell forming elements in the bone marrow The prompt and often extensive increase in the reticulocytes following the ingestion of liver left no doubt as to the efficacy of the therapy

The work of Minot and Murphy was rapidly confirmed by many observers both in North America and European countries and soon it received well deserved recognition As an award to which they were justly entitled they with George H Whipple received the Nobel Prize for Medicine in 1934

Although the effectiveness of liver therapy in pernicious anemia received wide acceptance its reception was not at first unanimous In this connection it is of interest to record the reaction of the late Dr Otto Naegeli Professor of Medicine in Switzerland probably the outstanding hematologist of his time as related by E Meulengracht (42) He says "He was not at all enthusiastic that is certain From the first day he took the position that this is not a causal but a symptomatic treatment, and that many cases did not respond to it" He circulated a questionnaire to 120 of his European colleagues and published the results in the *Folia Hematologica* in 1930 which were not entirely favorable It is not difficult to understand the skepticism of Naegeli for as he had observed so many times the natural course of the disease characterized by spontaneous remissions a certain amount of doubt was justifiable

W Richardson in 1928 (*45*) It should be kept in mind that Means had long been associated with Minot at the Massachusetts General Hospital and in addition to being a professional colleague was a close personal friend *In their article it is stated* The value of liver in promoting blood regeneration in an experimental chronic anemia due to blood loss is of course proved by the work of Whipple and it doubtless occurred to many when this work first appeared that a little liver now and then would be a good thing to include in the dietary of the patients with anemia Minot however took the hint of Whipple s work seriously to heart and went at liver feeding using large quantities in an entirely scientific manner "

The expectation in view of Whipples results, was that liver feeding if effective at all in human anemia would be effective in the secondary type *although Whipple himself (46) stated in 1925 that* even in the complex anemias (human pernicious anemia anemia with nephritis and cancer cachexia) food factors deserve serious consideration in the clinical management of the blood condition Means and Richardson (*45*) go on to say that Minot himself also for some years had had certain notions about the possible role of dietary errors in the genesis of pernicious anemia These were stimulated at least in part by an opinion expressed to him by the late James Homer Wright for many years pathologist at the Massachusetts County Hospital that the primary lesion of pernicious anemia was in the marrow and that it resembled a tumor This led *Minot to look elsewhere than in the increased blood destruction* for the cause of the disease To him the difficulty seemed to lie rather in the inability of the red blood cell elements to undergo normal maturation Means and Richards state further that This raised the question of growth promoting factors and the work of E V McCollum together with certain symptomatic resemblances between sprue pellagra and pernicious anemia and the already known beneficial effect of liver soup in the first of these and *finally Whipple s work all served to focus Minot s attention* on liver It is acknowledged by Minot and Murphy (*40*) that Whipple s work served as a stimulus to their investigation of liver as a form of treatment in pernicious anemia They say Following the work of Whipple and Robscheit Robbins we made a few observations concerning the influence of a diet containing an abundance of liver and muscle meat on blood regeneration The effect semed to be quite similar to that which they obtained in dogs *These observations together with the* information given above led us to investigate the value of a diet with an abundance of food rich in complete proteins and iron particularly liver and relatively low in fat as a means of treatment for pernicious anemia

It should be noted that others had fed a diet containing liver to patients with pernicious anemia and had reported improvement In no instance

In 1939 Wintrobe (*60*) reported that yeast would produce a maximal hematolopoietic response in some patients with pernicious anemia although the reason for this was not apparent

Additional experimental studies which had an important bearing on the development of our knowledge concerning this new vitamin were those of Stokstad and Manning (*61*) who found in 1938 that a diet containing all essential dietary elements known at that time was lacking in a growth factor for chicks A year later Hogan and Parrot (*62*) made the additional observation that chicks on such a diet developed a macrocytic hyperchromic anemia This work led to the important studies of Pfiffner and his associates which culminated in 1943 in the isolation in crystalline form of the substance which had been designated as B (*63*) and its conjugate (*64 65*) in 1945 These substances are now thought to be the same or closely allied to folic acid

The story of the development of our knowledge of the L casei factor is complicated and based on the excellent work of many investigators In 1940 Snell and Peterson (*66*) recognized that certain lactic acid bacteria required extracts of plants and animals for proper growth Mitchell Snell and Williams (*67*) in 1941 obtained a highly efficient growth factor for Streptococcus lactis R from spinach and on account of its source designated it as folic acid No further attempt will be made to give the details of all the fundamental investigations which ultimately led to the introduction of folic acid as a therapeutic agent in the macrocytic anemias A comprehensive review of this subject is given by Berry and Spies (*68*) to which the reader is referred

It was observed by Spicer Daft Sebrell and Ashburn in 1942 (*69*) that rats given either sulfaguanidine or sulfasuxidine at a 1 per cent level in purified diets developed leukopenia agranulocytosis and a hypocellular bone marrow The important discovery was also made that whole dried liver would prevent or cure these manifestations Ashburn Daft Endicott and Sebrell (*70*) in the same year noted that animals in whom these changes were produced had hyaline sclerosis and calcification of blood vessels necrosis of voluntary muscles and granulocytic aplasia of the bone marrow It was found by Kornberg Daft and Sebrell in 1943 (*71*) that certain liver fractions known to contain the L casei factor when given orally would correct the granulocytopenia and restore the red blood cells to normal in 10 days Furthermore Daft and Sebrell (*72*) in 1943 produced a striking leukopenia in rats with a sulfonamide diet and then caused the leukocytes to return to a normal level promptly with the administration of crystalline folic acid While these observations by the above workers in the United States Public Health Service were directed primarily toward the control of the granulocytes in the circulating blood nevertheless they had a most important bearing on the development of our knowledge concerning the relationship of folic acid to the activity of the bone marrow including the formation of the erythrocytes

The remarkable investigations of William B Castle and his collaborators which began in 1929 (*13*) and have continued to the present time (*49*) has led to the appreciation of the role played by the stomach in the production of the anemia of pernicious anemia The experiments which were brilliantly planned and executed have shown the importance between the deficiency of the gastric secretions the liver and normal hematopoiesis The results of Castle s experiment are epoch making and will continue for all time to be counted among the greatest advances in the study of disease processes The information thus made available served in part to direct the attention of Sturgis and Isaacs (*50*) to the normal stomach as a possible source of a potent antipernicious anemia medication This led to the introduction of ventriculin in 1929 (*50*) which has proved to be an effective form of medication

Of greatest significance in the development of measures for the treatment of pernicious anemia was the introduction in 1928 of a refined and highly potent liver extract by Edwin J Cohn and his associates (*51*) which is one of the most satisfactory forms of therapy, when given intramuscularly at the present time Important advances concerning the nature of the active material have been made by Randolph West and his associates (*52, 53*)

History of Development of Knowledge of Folic Acid in Relation to the Macrocytic Anemias—In 1932 it was observed by Wills and Bilimoria (*54*) that certain natives of India on a restricted diet developed a macrocytic anemia with a megaloblastic bone marrow This condition was relieved by the administration of yeast extract Three years later Wills and Stewart (*55*) by a dietary deficiency produced a macrocytic anemia experimentally in monkeys which was relieved by Marmite a yeast extract preparation A continuation of this work by Wills Clutterbuck and Evans (*56*) in 1937 led to their conclusion that the macrocytic anemia in monkeys thus produced was similar to the macrocytic anemia observed in natives of India They noted that yeast extract cured this type of anemia and published their paper with the title A New Factor in the Production and Cure of Macrocytic Anemias and its Relation to Haemopoietic Principles Curative in Pernicious Anemia

In 1935 Day Langston and Shukers (*57*) observed that an anemia and a severe leukopenia developed in young monkeys with a dietary intake deficient in vitamin B and possibly other essential organic substances Later a deficiency of a specific substance included in the vitamin B complex was postulated by Day and his associates as the cause of the syndrome and this was designated as vitamin M A continuation of these studies by this group led to the recognition in 1945 (*58 59*) that the administration of lactobacillus casei factor to monkeys with an experimentally produced macrocytic anemia caused a rise in reticulocytes followed by an increase in the white and red blood cells and hemoglobin to normal

and hematological response in patients with pernicious anemia. *This supports the hypothesis that such patients are unable to convert the conjugated to the free form which is effective in controlling the normal rate of maturation of the erythrocytes in the bone marrow.*

Spies and his associates (86) have suggested that if thymine is given to a patient with pernicious anemia in whom there is an absence of free folic acid it might be used directly in building nucleic acid. This substance might then be active in promoting the maturation of the erythrocytes in the absence of folic acid.

The Discovery and Introduction of Vitamin B_{12} into Medicine.—In 1947 Mary S. Shorb (87) of the Department of Poultry Husbandry of the University of Maryland published her observations which indicated that an unidentified factor (LLD) present in liver extracts was essential for the growth of Lactobacillus lactis Dorner. Furthermore this same observer reported several months later (88) that the concentration

TABLE XIV

AGE AT ONSET IN 147 PATIENTS WITH PERNICIOUS ANEMIA

Age at Onset	*Number*	*Per Cent*
40 Years or Later	133	90.5
50 Years or Later	106	72.1
60 Years or Later	52	35.4
70 Years or Later	15	10.2

TABLE XIV.—The above table indicates that pernicious anemia is a disease of middle life or later, as over 90 per cent of the patients have their initial symptoms at 40 years of age or later in life. It is not so rare to have the condition develop between the ages of 30 and 40 years and occasionally between the ages of 20 and 30 years, but cases in which the onset is below 20 years are extremely rare. In children the disease is practically unknown and any cases reported in a child of 10 years or less should be suspected of having some other form of anemia.

of this factor in liver extracts was in direct relationship to the potency of the liver preparations. At about the same time Randolph West observed (89) that this material which had been designated as vitamin B_{12} by Shorb was hematologically active when administered intramuscularly to patients with addisonian pernicious anemia. He noted that promptly after the injection there was the characteristic reticulocyte response and shortly thereafter a rise in the hemoglobin content and red blood cell count of the peripheral blood similar in all respects to the changes observed following the injection of liver extract in such patients.

The isolation of vitamin B_{12} as a red cobalt containing compound was reported simultaneously in 1948 by Rickes and his associates in the United States (90) and by E. Lester Smith in England (91). An excellent review is given by Smith (92) of the steps leading to the isolation of the vitamin by the method of partition chromatography employed by him. The surprising fact that the purified substance contained cobalt

In 1945 Angier and his associates (73) reported that they had synthesized a compound which was identical with the L casei factor isolated from liver From the data which they furnished it was apparent that the synthetic compound was exactly the same in its chemical constitution and physiological action as the natural product This group in 1946 (74) reported on the chemical composition and methods of synthesis of L casei factor

The Introduction of Folic Acid into Clinical Medicine in the Treatment of the Anemias—In 1944 Sharpe VonderHeide and Wolters (75) administered vitamin B concentrate obtained from yeast to 10 patients with pernicious anemia At the end of four weeks treatment there was a slight increase in the hematocrit readings but otherwise it was reported that no important changes occurred in the blood

In 1944 Castle (76) and his associates made certain observations which led them to conclude that folic acid among other substances tested was not effective in reconstituting vitamin free casein as the extrinsic factor It was asserted however that the extrinsic factor could still be reasonably regarded as an unidentified thermostable component of the vitamin B complex

The first publication in which it was stated that crystalline folic acid is effective in the treatment of macrocytic anemia of humans is the one by Spies Vilter Koch and Caldwell (77) which appeared in November 1945 These observers administered synthetic folic acid (L casei factor) intravenously to 5 patients with a macrocytic anemia and noted an immediate clinical improvement which was associated with reticulocyte response and an increase in the red blood cells in a manner entirely comparable to that observed in patients with pernicious anemia following the injection of potent liver extract Furthermore the same material was given orally to 4 additional patients with macrocytic anemia in doses of 50 milligrams two or three times daily They all responded favorably A number of publications (78 78A 79 80 81 82 83 83A) which appeared shortly thereafter amply confirmed the statements of Spies and his associates

It was Vilter and his co workers (84) who first pointed out that folic acid in the doses commonly given since the time of introduction of the substance as a therapeutic agent and to the time of their report was less effective than intramuscular liver extract in the treatment of the neurological manifestations of pernicious anemia

Bethell and his associates (85) demonstrated that vitamin B conjugate is ineffective when administered to patients with pernicious anemia and those with a macrocytic anemia following total gastrectomy Of great importance is the observation which this group made that when the conjugated form is acted upon by means of a specific enzyme and converted to the free form it is capable of producing a significant clinical

other form of macrocytic anemia such as that due to diminished intake of the extrinsic factor to subleukemic leukemia hemolytic anemia aplastic anemia or the megaloblastic anemia of infancy The youngest bona fide case I have observed was in a girl age 19 years who had experienced the earliest symptoms three years previously Her case fulfilled all of the rigid diagnostic criteria of the disease including a very favorable response to antipernicious anemia therapy She is still under our observation and treatment at the age of 39 years It is interesting to note that her hair became streaked with gray at the age of 14 years

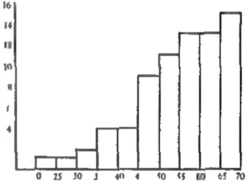
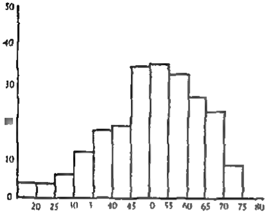


Fig 20—Age of onset of pernicious anemia in 220 patients arranged with reference to the number of persons living in the various decades Ordinate cases per 100 000 individuals of the same age abscissa age of onset There is a steady rise in the comparative incidence of the ages of onset As stated by Meulengracht (96) Pernicious anemia can thus be shown to be distinctly a disease of old age with a period of manifestation which is not ended at the age when death on the average occurs (Meulengracht courtesy *American Journal of Medical Science*)

The literature dealing with pernicious anemia in infancy and childhood has been reviewed by Peterson and Dunn (97) They separate such patients into two groups namely those with the complete clinical picture of pernicious anemia and those having the changes in the circulating blood of pernicious anemia but not requiring continuous treatment In my opinion many in the latter group should be considered as having the megaloblastic anemia of infancy In a review of the American literature to 1946 and the foreign publications to 1942 Peterson and Dunn (97) were able to find reports of two cases in childhood and infancy who appeared undoubtedly to have pernicious anemia These patients were 13 years and 13 months of age respectively Their own case which they considered as having pernicious anemia was an infant 13 months of age whom they followed until the age of five and one fourth years

An intensive study of an infant with macrocytic anemia which extends from infancy for over a decade is reported by Benjamin (98) His patient had a disease which was undoubtedly characteristic of pernicious anemia in many respects There were two differences pointed out by the author however which strongly suggests that the patient did not have pernicious anemia They were first the achlorhydria was not persistent which in my opinion would eliminate the diagnosis of pernicious anemia and second there was no tendency to spontaneous re

Fig 19 —This chart shows the age distribution of 220 cases of pernicious anemia arranged according to decades The ordinate shows the number of cases in each group and the abscissa the age at which the disease first manifested itself The diagram shows that the onset occurred in the largest number of cases between the forty five and sixty five years with a decrease after the sixty fifth year It is pointed out by Meulengracht (*96*) that this decrease is not a true one for the actual number of persons living in the older age groups are less As Meulengracht says "On account of this decrease in the number of elderly persons any characteristic—in our case pernicious anemia—must have fewer examples in old age Reference to Figure 20 shows the same data arranged in relation to the total number of individuals of each age group in the population When this factor is taken into account it indicates that pernicious anemia is a disease of old age (Meulengracht courtesy *American Journal of Medical Sciences*)



as an essential part of the molecule was made at the same time by Rickes and his associates (*93*) and by E Lester Smith (*92*)

Of great interest and practical importance was the discovery by Rickes *et al* in 1948 (*94*) that vitamin B_{12} is produced by a mold Streptomyces griseus and that the vitamin can be isolated from the nutrient fluid in which the organism is grown

In 1948 E Lester Smith provided evidence which indicated that vitamin B_{12} is made up of a group of factors probably all clinically active rather than one factor alone (*95*)

Etiology—Age—Manifestations of pernicious anemia most commonly develop between the ages of 45 and 60 years and hence the disease must be considered as having about the same age distribution as that of cancer It should be emphasized however that old age plays a more important role in the etiology than is commonly recognized Meulengracht (*96*) has demonstrated clearly that if the age of the onset of the *earliest symptoms is correlated with the number of persons who are living* in the various decades of life the disease is distinctly one of later life With the present rate of increase in the span of life one is more likely to observe in the future even more cases in elderly persons This situation *is well shown by the figures (Figs 19 and 20) reproduced* from an article dealing with this topic by Meulengracht (*96*)

It is improbable that true pernicious anemia occurs in infancy or childhood although cases have been reported in the first decade of life *It is more likely* however that such patients have suffered from some

Sex Incidence—Although opinion has been divided on this question it is now established that there is no significant difference in the incidence of the disease in the two sexes Cabot (*104*) in 1915 in considering a group of 1157 cases of pernicious anemia found that 723 were males and 434 females On the other hand figures from Europe show the reverse Cornell (*105*) in 1927 in a survey of figures from widely separated countries found that of 1726 cases 819 occurred in males and 907 in females In our own series of approximately 1200 patients the sex distribution was almost equal Davidson and Gulland (*106*) also concur in the statement that there is no important difference in the sex incidence in their series 141 were males and 159 females

Geographical and Racial Distribution—It has been clearly established that there is a racial and hence a geographical distribution of pernicious anemia All observers agree that it is distinctly a disease of the white race in temperate climates It is therefore more prevalent in England Wales Scotland Ireland Germany France the Scandinavian countries Canada and the northern United States and is less common in the countries of southern Europe It is unknown in natives of the tropics Azmy Pasha and Zanaty (*107*) state that it is rarely observed in Asiatics They likewise found it to be extremely uncommon in Egypt for after investigating many cases of anemia only one bona fide instance of the disease was found

It is known to be less prevalent in the Negro race Some contend that full blooded negroes never have the disease although it does occur in mulattoes I have never seen the condition in a negro of pure blood One patient of negro descent age 61 when first observed certainly had the disease and although the black pigmentation of his skin was typical his features were not negroid Furthermore he proudly showed his Bible with the family record which indicated that his great great grand mother was a white Scotch woman That the condition does occur in negroes *or at least mulattoes* is indicated by the observations of various authors Kampmeier and Cameron (*108*) found the ratio of negroes to white patients with pernicious anemia to be one to seven at the Charity Hospital in New Orleans McCracken (*109*) estimated that approximately *3 per cent of all persons with pernicious anemia are negroes* but he concluded that it is doubtful if the malady ever occurs in full blooded members of that race It is the opinion of Grandy (*110*) that the condition is not as uncommon in negroes as has been commonly supposed Evans (*111*) at the Johns Hopkins Hospital found nine instances of pernicious anemia in negro patients in a total number of 578 admissions for the disease All of his patients were mulattoes

It is also rarely present if ever in the Chinese The late Francis W Peabody who had a great interest in the disease told me that in a year spent as visiting Professor of Medicine at the Pekin Union Medical

missions The author regarded the condition in this patient as due to a congenital absence of the intrinsic factor

An undoubted case of pernicious anemia in a girl of 14 years is reported by Hamilton and Fowler *(99)* This case seems to fulfill the most rigid diagnostic requirements The anemia was macrocytic and hyperchromic in type the mean corpuscular volume and mean corpuscular hemoglobin values were increased the bone marrow was megaloblastic leukopenia and thrombopenia were present there was hyperbilirubinemia and a persistent histamine resistant achlorhydria, gastroscopic examination showed a severe atrophic gastritis and both liver extract and pteroyl glutamic acid maintained the patient in complete remission The patient's mother had subacute combined degeneration of the spinal cord and achlorhydria

The case of a six year old girl with a macrocytic anemia a megaloblastic bone marrow a specific response successively to refined liver extract folic acid and vitamin B_{12} and the need of continuous treatment to maintain a remission is reported by Davis and his associates *(100)* There were no neurological complications A small amount of free hydrochloric acid was present in the gastric juice following the injection of histamine This finding in my opinion eliminates the diagnosis of true addisonian pernicious anemia

While in rare instances cases in infants have been reported as true examples of pernicious anemia it is advisable to regard all patients in whom this diagnosis is entertained with suspicion if they are under 14 years of age and to keep in mind that even in the second decade of life the disease is exceedingly rare

Frequency —Pernicious anemia must be regarded as a disease of relatively common occurrence in North America for in every general hospital there are usually three or four patients with the disease for every 1000 patients admitted At the Henry Ford Hospital in Detroit this proportion was 2 2 per 1000 *(101)* According to Friedlander *(102)* there were 80 415 patients admitted to the Peter Bent Brigham Hospital in Boston in the interval between April 1913 and November 1932 a period of approximately 19 years During this time 500 cases of pernicious anemia were seen which gives a ratio of one patient with this variety of anemia for every 161 admissions or about 6 per 1000 Askanazy *(103)* in 1937 gives the incidence in the population at large as 6 9 per hundred thousand in the United States 9 1 in Canada and 9 18 in Sweden no cases were reported in Java over a period of 20 years

There are at least two explanations for the apparent present day increase in the disease namely (1) Accurate diagnostic methods are more widely applied and (2) As a result of increased longevity a greater number of persons are now living to the age when the disease commonly occurs

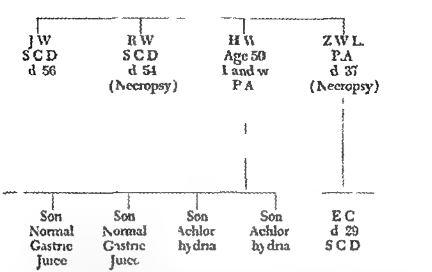


Fig 21.—Showing a family in which there were 5 cases of pernicious anemia in two generations In addition two sons were known to have an achlorhydria although they were free from symptoms and two other sons had normal gastric juice It is our present belief that the sons with normal gastric juice will probably never develop pernicious anemia whereas the two with an achlorhydria are likely candidates for the disease provided some unknown precipitating factor becomes active P A = pernicious anemia S C D = Subacute combined degeneration of the spinal cord.

incidence of 7 9 per cent In this group there were three families in which three of the children had the disease and in five additional families there were cases in three or more members of the same family in successive generations among the lineal or collateral descendents In one family there were identical twin sisters the only siblings age 35 years who had the disease In another family of four children two brothers died of the disease and in two sisters the diagnosis had been made In a study of 377 patients with pernicious anemia at this Institute Dr Lloyd R Gates asked each patient "Did any of your relatives have anemia?" Of these 27 3 per cent answered "Yes" whereas in 536 control patients of similar age who did not have the disease only 9 1 per cent answered in the affirmative Schemm (*115*) reports a remarkable family in which five of the seven children definitely have proven pernicious anemia One sister showed no evidence of the disease and free hydrochloric acid was present in the gastric secretions and one brother would not submit to an examination

Askey (*116*) has summarized previous studies on the subject and among other things emphasizes and confirms the work of previous observers that anacidity is more common among the relatives of patients with the disorder than in the population at large He found that there was an increased incidence of anacidity particularly among the blood relatives in the two decades prior to the age of 40 years and about a double percentage among the near relatives as opposed to distant relatives

School in China he did not observe a single case of pernicious anemia among the native Chinese despite his careful search for it in many patients whom he examined

Influence of Solar Radiation —It was first emphasized by Smith (*112*) that there is a significant relationship on a geographical basis between *the relative lack of solar radiation and mortality* from pernicious anemia in the United States prior to liver therapy Apperly (*113*) has investigated this subject and warned that other associated determining factors should be taken into account Among these he includes altitude dust various individual and racial differences and possibly unknown conditions To obtain more definite evidence bearing on this question he investigated the incidence of skin cancer which is known to occur more frequently in regions with the greatest solar radiation *His observations* indicated that the incidence of skin cancer has an inverse relationship to that of pernicious anemia The author states that Argentaffin granules para amino benzoic acid melanin insulin and sex hormones are all composed chemically of benzene or aromatic rings and suggests that these substances are dependent for their formation upon an adequate production of dihydrophenylalanine through the agency of solar radiation In his opinion this possibility may be of significance when one recalls that there is a relatively high incidence of pernicious anemia in blonde and prematurely gray persons who are often of a eunuchoid type, and that the disease is not infrequently associated with diabetes While these relationships are of great interest and the results suggestive from a theoretical standpoint investigations regarding them should be continued further before any concrete conclusions are drawn

Recently Thiersch (*114*) has concluded that in South Australia there is no evidence to indicate that an inverse relationship exists between the incidence of pernicious anemia and the degree of solar radiation His observations therefore fail to confirm those of Smith and Apperly

Heredity —In more recent years it has been agreed by practically all students of the disease that there is a definite familial incidence and that hereditary factors undoubtedly play an important role in the etiology of the condition Davidson and Gulland (*106*) have calculated that the chance of any one individual acquiring pernicious anemia are 1 to 20 000 Examples of the condition occurring in a number of blood relatives therefore are overwhelmingly in favor of a familial incidence as opposed to chance

It is generally stated that in between 10 and 20 per cent of the cases another instance of the malady is present in one or more of the blood relatives This is probably an underestimate as it is often impossible to obtain an adequate family history In an analysis of our own 654 cases some years ago it was found by Stamos (24) that in 51 instances there was another case in a consanguinous relative which gives a familial

In a more recent study Neel (unpublished data) states that it is difficult to explain the findings in relatives of patients with pernicious anemia in terms of formal genetics Although it has been suggested that the tendency to develop achylia in relatives may be on the basis of a single dominant gene the data can also be interpreted as illustrating the effects of an irregularly expressed common recessive gene with the apparent dominance due to the marriage of a homozygous (achylic) individual with a heterozygote (normal) person He believes it is probable that the development of achlorhydria may be precipitated by both environmental and genetic factors with the latter possibly multiple In his opinion it is not clear whether all individuals with achylia are equally prone to develop pernicious anemia or whether there are further genetic restrictions

The occurrence of idiopathic hypochromic anemia and pernicious anemia in the same families with a frequency which cannot be accounted for on a fortuitous basis and also well authenticated instances in which these two diseases have occurred in the same person suggests strongly that they may have a common inherited cause As idiopathic hypochromic anemia is due to an iron deficiency and achlorhydria contributes to it because it results in an impaired absorption of the metal it is not surprising that the two diseases should coexist in the same patient as free hydrochloric acid is usually absent from the gastric secretions in both diseases Furthermore as achlorhydria is present more commonly in the relatives of patients with pernicious anemia than in the population at large it is to be expected that idiopathic hypochromic anemia would be more likely to occur in the relatives of patients with pernicious anemia for this reason Heath (*119*) summarizes the literature in regard to the familial occurrence of the two diseases and reports a family in which three sisters with achlorhydria had both pernicious anemia and idiopathic hypochromic anemia Furthermore there was evidence of borderline anemic states in other members of the family while several had either pernicious anemia or idiopathic hypochromic anemia

Physical Factors—It is believed by many that persons who develop pernicious anemia have certain constitutional factors which are characteristic of the disease According to Draper (*120*) both the male and female patients approach the acromegalic group as they have a tendency toward a massive lower jaw in proportion to the other facial measurements and in addition have a deep broad and short thorax with a wide subcostal angle *In his opinion there is a remarkable similarity of the body build* in male and female patients with this disease Bauer (*121*) however does not agree with Draper that patients affected with pernicious anemia approach the acromegalic in physical measurements He believes that such a claim requires confirmation on a large scale

It has long been established that persons with light hair a fair complexion and eyes of the lighter colors are more prone to have the condi

In summary then the estimated familial incidence of between 10 and 20 per cent the occurrence in identical twins the observation that as many as five cases can occur in the same family in the same generation the increased incidence of anacidity especially in near relatives the fact that there are a significantly greater number of cases of anemia in the families of patients with pernicious anemia than in a similar group without the disease all provide strongly suggestive evidence that hereditary factors play an important role in the pathogenesis of the disease

Further information derived from future observations is necessary before any definite conclusions can be drawn concerning the more precise nature of the hereditary trait which is transmitted The view has been submitted but is unproven that the disease is a dominant characteristic dependent on [redacted] single gene and that there are members of families who do not have pernicious anemia but act as carriers of the condition from the standpoint of heredity These persons do not have the fully developed disease but some evidence of it in the form of glossitis atrophy of the papillae of the tongue and anacidity It is believed by some that there is a hereditary defect in the stomach which is transmitted from one generation to another On the other hand Cooley *(117)* makes the suggestion that two genes may be involved one affecting the stomach and the other the bone marrow There is no evidence that the disease is sex linked

According to those who have made a study of genetics consanguineous marriages are of value in establishing the hereditary characteristics of a disease as they accentuate the recessive traits They are however of no particular value one way or another if the trait is dominant The remarkable instance cited by Askey *(116)* of the marriage of two cousins who had 13 children of whom five had pernicious anemia (four authenticated) is suggestive but not conclusive that the trait is recessive

The subject of heredity in pernicious anemia has been investigated by Neel *(118)* and the entire subject reviewed It is his opinion that the tendency to achlorhydria in patients with this disease appears to behave as if it is due to a dominant factor with irregular expression He further states that from the work of various investigators the problem which has gradually emerged is one of the inheritance of a defective gastric and possibly duodenal mucosa The appearance of such mucosa in kindreds is probably controlled largely by one or more dominant genes Individuals with the inherited defect are detected most readily by achlorhydria or achylia Some persons with a defective mucosa and achlorhydria develop pernicious anemia some idiopathic hypochromic anemia and others probably a great majority remain asymptomatic The increased possibility of a patient with pernicious anemia developing carcinoma of the stomach [redacted] well recognized and here again this appears to be associated with the defective gastric mucosa

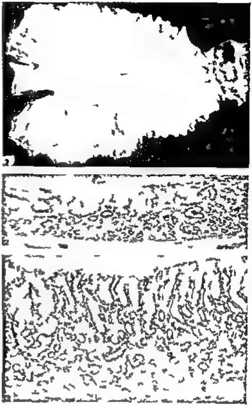


Fig 22 —No 1 shows the stomach from a patient age 62 who had a macrocytic hyperchromic anemia with a red blood cell count of 2 6 millions per cubic millimeter and slight demyelinization of the fibers in the posterior column of the spinal cord There was a history of a similar anemia which had been regarded as true pernicious anemia 3 years previously and which had disappeared following liver therapy During the recurrence liver therapy *had been given only three days before death* The stomach opened *along the greater curvature* showed a very thin fundic zone with easily visible submucosal vessels contrasted with the pyloric zone of normal thickness except for a single polypoid nodule

No 2 shows a section of the fundic portion of the gastric mucosa from a patient who died of pernicious anemia The architecture is irregularly arranged with small tortuous glands entirely devoid of parietal and chief cells × 92

No 3 is a section of the normal pyloric portion of the gastric mucosa from the same case as shown in No 2 (Cox courtesy *American Journal of Pathology*)

It was observed by Castle and his collaborators (*127*) that when either 200 grams of beef muscle or 150 cc of normal human gastric juice was administered *singly* to patients with pernicious anemia there was no effect on red blood cell production as shown by an increase in the reticulocytes of the circulating blood The *simultaneous* administration of beef muscle and gastric juice however produced a significant rise in the reticulocyte count the hemoglobin and red blood cell count of the circulating blood It was concluded therefore that the increase in blood production depended upon two factors one present in beef muscle designated the *extrinsic factor* by Castle and the other the *intrinsic factor* present in normal human gastric juice As emphasized by this investigator the negative effect of the beef muscle when given alone to patients with pernicious anemia indicated that *in patients with pernicious anemia there is a diminution or absence of the gastric or intrinsic factor*

It was observed further by this observer that in order for the combination of beef muscle and gastric juice to produce an effect on the blood the two factors must come in contact with each other at or near a neutral

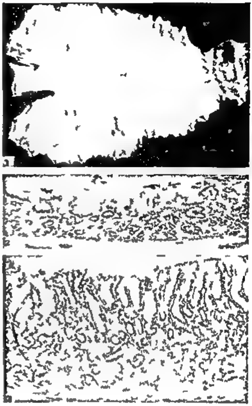
tion than those who are dark complexioned Frequently patients with the disease have prematurely gray hair which commonly becomes apparent before the age of 30 years Gray hair was observed in one of our patients at the age of 19 years There is also often a family history of prematurely graying of the hair Evidence that this change in the hair occurs relatively early in patients with pernicious anemia is shown by the figures of Hardgrove and his associates (*122*) who found that 14 per cent of their group of 60 patients had gray hair before the age of 30 years In one of their patients in whom the disease was recognized at the age of 39 years it is stated that her hair was white during the acute stages of her illness and with treatment it turned dark brown Such a change has never been observed in my experience

While the above remarks pertaining to the predominance of certain physical characteristics in patients with pernicious anemia have received general acceptance it should be emphasized that the disease is *not* strictly limited to persons with certain physical or racial characteristics If sufficient positive findings are present in any given case the diagnosis of course should be made regardless of the absence of the physical make up or of the racial origin of the patient in question

The Present Day Theory Relating to the Etiology of Pernicious Anemia —With the exception of Samuel Fenwick, who as early as 1877 (*9*) considered the degenerative changes in the stomach to be of importance the early descriptions of the disease did not contain any statements having an important bearing on the etiology of the disorder Relatively early in the history of the condition however two main views developed concerning the mechanism of the cause of the anemia The first based upon the studies of the bone marrow by William Pepper (*26*) and supported by Cohnheim (*123*) and Ehrlich (*124*) regarded changes in the bone marrow as the major cause of the anemia An opposing view largely championed by William Hunter in England (*11*) and generally accepted in English speaking countries at the time held that the anemia resulted from an increased destruction of blood

With the modern contributions of Minot and Murphy Peabody Castle and others the view that the primary cause of the anemia of pernicious anemia is a maturation defect of the red blood cells has gained ascendency although the possibility of an associated increased destruction of the red blood cells at least as a mechanism of secondary importance must be given consideration

Castle's Theory of the Etiology of Pernicious Anemia —Beginning in 1928 (*125*) and continuing (*126*) William B Castle conceived and carried out with his associates a series of brilliant experiments which shed more light on the etiology of pernicious anemia and incidentally on at least one phase of the control of red blood cell formation than all previous efforts had accomplished in the entire history of medicine



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It was observed further by this observer that in order for the combination of beef muscle and gastric juice to produce an effect on the blood the two factors must come in contact with each other at or near a neutral

reaction within the alimentary tract He demonstrated in support of this that if the beef muscle and gastric juice are given within six hours of each other the hematopoietic effect may occur but if the time between the administration of the two is as long as 12 hours there is no effect Furthermore when the beef gastric juice mixture is given at a pH of 1 8 to 3 5 no hematopoietic effect is observed if it is brought to a point between 5 and 7 however it is effective The fundamental conclusions stated by Castle remain valid although additional information has amplified and extended his original deductions

Changes in the Stomach —When the stomach of a patient with pernicious anemia is examined at necropsy it has been found by Magnus and Ungley *(128)* and Meulengracht *(129)* and Cox *(130)* that the mucous membrane of the fundus portion is reduced in thickness to about one half that of the other areas Furthermore microscopic examination reveals that the normal chief and parietal cells are absent the mucosal glands are shorter less numerous and more tortuous than in the normal fundic region In addition Fox and Castle *(131)* proved beyond the question of a doubt that the fundic area of human stomach has anti pernicious anemia properties when fed to patients with the disease, which now makes it clear that this zone is at least the principal site of the formation of the intrinsic factor This is in accord with the knowledge that this area is found to show degenerative changes in patients dead of the disease In the hog however Meulengracht *(132)* has demonstrated that the pyloric regions rather than the fundic is the site of formation of the intrinsic factor

More recent studies by Landboe Christensen and Plum *(133)* have been made by feeding patients with pernicious anemia in relapse dried powdered preparations made from the fundal and pyloric parts of the wall of the human stomach In the doses used fundus powder gave a maximal response and pylorus powder showed moderate activity The glands which secrete the intrinsic factor therefore are apparently not as sharply localized in the gastric mucosa as previous investigations have suggested *In humans therefore it appears to be established that the primary and chief cause of the anemia of pernicious anemia is a degenerative change in the glands of the mucous membrane of the stomach more in the fundic than the pyloric region with a resultant failure to secrete a normal amount of the intrinsic factor*

The cause of the deranged function of the stomach however is obscure Apparently it is not inflammatory in nature and undoubtedly it may vary in intensity as remissions are commonly seen in the spontaneous course of the disease Undoubtedly there is a hereditary factor but the immediate precipitating cause is wholly unknown at present (For additional discussion concerning the changes observed in the stomach see pages 274 and 276

In addition to the decrease in the intrinsic factor there may be other changes which play an important but secondary etiological role. Evidence indicates that the formation of an adequate amount of erythrocyte maturing factor depends upon an ample diet and the preservation of a number of functions, namely, secretion of a normal amount of intrinsic factor, the permeability of the intestines so that the E M F may be absorbed in normal amounts, capacity of the liver to store the E M F, and the ability of the bone marrow to function in response to the influence of this substance. (The influence of these various factors is represented diagrammatically in Figure 23.)

In pernicious anemia it is generally accepted that the primary cause is a decrease in the amount of the intrinsic factor, but in addition it is probably true that a diminution in the extrinsic factor in the diet may also play a role of secondary importance. The importance of the extrinsic factor is indicated by the report of Wintrobe (*134*) that about one third of the patients with pernicious anemia will respond to yeast which is known to be a good source of this material. It is probably true that this response to yeast results from the administration of an excess of extrinsic factor in the presence of a greatly diminished but not completely absent intrinsic factor (*135*). That liver damage, malabsorption from the intestine, and the failure of the bone marrow to respond to the E M F may contribute importantly to the cause of the anemia is unlikely in most cases of true pernicious anemia.

The Extrinsic Factor.—The chemical and physical properties of the heat stable extrinsic factor are not known in any great detail. It has been found by Formijne (*136*) to be present in a 70 to 80 per cent alcoholic extract of meat. Fats and lipoids can be removed from this extract without loss of activity and the extrinsic factor in the extract will pass through an ultrafilter. He also found that less than 50 per cent of the extrinsic factor was present in the precipitate obtained by saturation of the extract with ammonium sulfate. Various investigators have found that it is present in a wide variety of substances, dietary and otherwise, as follows: beef muscle (*127*), milk (*137*), eggs (*138, 139*), rice polishings (*126*), wheat germ (*126*), liver (*140*), yeast (*141*), Cohn's fraction G of liver extract (*142*), and the acid hydrolysate of liver extract (*126*). There is also evidence to suggest that it is present in tomatoes (*125*) and that it may be deficient in wheat gluten and both animal and yeast nucleic acids (*141*). Although Wilkinson *et al.* (*143*) claim that a reaction can occur between the extrinsic and intrinsic factors in vitro, this is denied by Formijne (*136*).

The lack of potency of riboflavin (*141*) and nicotinic acid (*142*) have already been reported. In a more recent study of the extrinsic factor by Castle and his collaborators (*144*) it has been observed that the active material which acts as the extrinsic factor can be removed from beef

muscle by repeated extraction with dilute acetic acid and that it is resistant to autoclaving and alkalinization. These investigators found that extrinsic factor can be removed from crude casein by repeated precipitation or by extraction with dilute acid or with alcohol. Such procedures tend to remove also the known members of the vitamin B complex.

It has been shown recently that the extrinsic factor can be separated from beef muscle proteins or casein with dilute acetic acid or alcohol *only* by prolonged extraction with alcohol. This suggests the properties of the animal protein factor, a substance which is either identical or closely related to vitamin B_{12}. Furthermore, although *vitamin B_{12} is* of uncertain action when given orally, it can be activated by incubation with normal human gastric juice in a manner in which known extrinsic *factor can undergo the same activating change. These observations* suggest strongly that vitamin B_{12} is either closely allied or identical with the extrinsic factor.

The Intrinsic Factor.—The exact nature of the intrinsic factor is not known. It is believed to be secreted in man chiefly by the glands of the cardiac and the fundus regions of the stomach *(131)*. Studies have shown that it is not hydrochloric acid or any of the known ferments of the gastric juice such as pepsin, rennin or gastric lipase. When heated to boiling for five minutes or exposed to a temperature of 70 to 80 degrees for one half hour it is destroyed. It is not present in saliva or the duodenal contents. The addition of alkali to the gastric secretions in amounts which bring the pH to 10 does not inactivate it, but it is inactive when the pH is below 3.5 in vivo.

A parallel has been shown to exist by Taylor and his associates *(145)* *between the proteolytic activity on casein of normal human gastric juice* at a pH of 7.4 and the activity of the intrinsic factor. A concentrate prepared from hog's pyloric mucosa by Agren and Waldenstrom *(146)* containing *alpha aminopolypeptidase activity has led these investigators* to suggest that this latter substance might be the intrinsic factor. A similar enzyme prepared by Fruton *(147)* from thymus, however, failed to display this activity.

Although the exact nature of the intrinsic factor is unknown at present, it is believed by Castle and his collaborators *(145)* to be an enzyme which functions best at a pH of 7.4 to 7.7. Davidson and Davis *(148)* consider it to be a proteolytic enzyme, Mazza and Migliardi *(149)* a prolinase and Agren *(150)* an aminopolypeptidase. Evidence in support of Castle's view appears to predominate.

Prusoff, Welch, Heinle and Meacham *(150A)* consider that the effect of the intrinsic factor is to increase absorption of vitamin B_{12}. They do not believe it is possible to state how this is accomplished. It is their opinion that the true relationship must await further purification of the intrinsic factor. Furthermore, the present evidence does not justify the

belief that there is a relationship between the capacity to bind vitamin B_{12} and intrinsic factor activity A comprehensive review with a bibliography of 125 articles dealing with the development of our knowledge concerning the gastric intrinsic factor and its relation to pernicious anemia has recently been published by Castle (*150B*)

The Reaction between Extrinsic and Intrinsic Factors—It was Castle s original idea that some type of reaction occurred between the intrinsic and extrinsic factors to form the new thermolabile compound the liver principle It is possible in keeping with the observations of Ternberg and Eakin (*151*) that the extrinsic factor combines with the intrinsic factor of the gastric juice to form a compound which is resistant to the destructive action of the alimentary tract bacteria The fundamental observations of these investigators have been confirmed by Ungley and Cuthbertson (*152*) More recently however the view is becoming more generally accepted that the intrinsic factor serves to expedite the absorption of the extrinsic factor from the gastrointestinal tract (*153*)

There is convincing evidence against the earlier belief that *a chemical reaction occurs* between the extrinsic factor and intrinsic factor to form the heat stable active liver principle or erythrocyte maturing factor (E M F) for example if the two factors are incubated in vitro for a period of 12 hours and then brought to the proper pH the material is hematopoietically active This is not however because a heat stable liver principle has been formed because if such a mixture is heated to 100 degrees (C) the activity is destroyed Although Wilkinson *et al* (*143*) claimed that such a reaction can occur between the two factors in vitro subsequent work by Formijne (*136*) has not substantiated this Furthermore it has been shown by Gardner and his associates working in Castle s laboratory (*153*) that when a 70 per cent alcoholic extract of beef muscle (extrinsic factor) is given intravenously to a patient with pernicious anemia without contact with gastric juice at any time there is distinct evidence of hematopoietic activity Thus the important fact appears to have been demonstrated that the extrinsic factor *alone* when given intravenously *can act directly as the antipernicious anemia factor* Obviously such an important experiment strongly suggests that the function of the intrinsic factor is to facilitate absorption of the extrinsic factor and furthermore that the extrinsic factor and the liver principle are probably the same substance both of which are heat stable and soluble in 70 per cent alcohol

It is likely therefore that the main function of the intrinsic factor of gastric juice is to make possible the absorption of the extrinsic factor in some as yet undetermined manner That the two factors interact to form a heat stable compound the liver principle is unlikely Two possible mechanisms previously mentioned may explain the purpose of the intrinsic factor It 1 may in some unknown manner expedite the

absorption of vitamin B_{12} which is now generally considered to be the extrinsic factor or 2 in keeping with the work of Ternberg and Eakin (*151*) it may unite to form a compound which *is resistant to the action* of the intestinal bacteria and thus prevent its destruction in the gastro intestinal tract Some support is given this idea by the work of Watson *et al* (*154*) who found that the administration of aureomycin which destroys intestinal bacteria caused a hematopoietic response in patients with pernicious anemia This work however is not confirmed by the observations of Ungley (*155*) who in addition to studying the blood made careful bacteriological studies of the stools and determined that bacteria in the intestinal tract were eliminated When such a condition was produced it was *not* found contrary to the report of Watson that there was a response in the blood In the observations of Watson, however the reticulocyte response did not occur until between the 20th and 30th days of treatment whereas Ungley s experiment was terminated after 10 days The experiments of Watson therefore await refutation or confirmation with exact duplication of her experimental procedure

Further studies to determine if vitamin B_{12} could be absorbed provided the destructive action of the intestinal juice could be reduced or eliminated have been made by Ungley (*156*) He applied 5 micro grams daily to the buccal mucous membrane and instilled vitamin B_{12} with and without gastric juice into a washed segment of intestine isolated between two balloons of a Miller Abbott tube These experiments led to negative or trivial results In the opinion of Ungley (*156*) these nega tive findings when considered with his studies following the sterilization of the intestinal tract are against but do not entirely exclude the possi bility that Castle s intrinsic factor acts by protecting vitamin B_{12} from destruction in the gastro intestinal tract

In collaboration with Bethell it has been observed by Hall (*157*) in confirmation of previous studies of Berk *et al* (*158*) that orally administered vitamin B_{12} for its *effective* utilization requires the presence of a potentiating agent such as the intrinsic factor of Castle In the absence of this agent the hematopoietic responses even in doses *100* times the minimal effective parenteral *dose* are *variable and un* certain Potentiation can be provided not only by normal gastric juice but also by extracts of the stomach and intestines of swine It is not *possible* is yet *however to produce consistently effective* and reliable therapeutic results with such preparations apparently due to the ease of destruction of the intrinsic factor during the concentrating process of the gastric and duodenal substances These observers believe that their studies support the concept that the intrinsic factor is enzymic in nature

It has been reported by Ungley (*159*) that possibly a certain amount of vitamin B_{12} can be absorbed without first coming in contact with the intrinsic factor This suggestion arises from his observation that there

is some response to the oral administration of single doses of 3000 micrograms of the vitamin One view is that such responses result from the interaction between the orally administered vitamin and slight traces of intrinsic factor which may remain in the gastric juice a view which is still sound in my opinion Ungley states however that at least 500 cc of normal gastric juice is required to insure an adequate hematopoietic response from even 50 to 80 micrograms of orally administered vitamin B_1 If this is correct the equivalent volume in terms of pernicious anemia gastric juice would be enormous and beyond the secretory capacity of the trophic stomach mucous membrane in such patients In his opinion it would be surprising if a patient with pernicious anemia secreted a sufficient quantity to combine with more than two milligrams however large the dose of vitamin B_1

At the present time therefore it appears logical to assume that the main function of the intrinsic factor in gastric juice is to facilitate the absorption of the extrinsic factor (vitamin B_1) In pernicious anemia the chief defect is the diminution or absence of this factor This interferes with the proper absorption of vitamin B_1 and consequently as it is probably also the active liver principle a disturbance in red blood cell maturation results and the characteristic picture in the blood develops

Vitamin B_1 the Antianemic Principle of Liver (Erythrocyte Maturing Factor)—In 1926 Minot and Murphy demonstrated conclusively for the first time that the feeding of 250 to 500 grams of liver daily controlled the anemia of pernicious anemia Several years later Castle (1929) and his associates developed the theory that the antianemic principle of liver was formed by the interaction of the extrinsic of the diet with the intrinsic factor normally secreted by the glands of the stomach In 1927 Cohn and his collaborators (*51*) developed a method whereby a concentrated liver extract designated Fraction G could be prepared which served as an oral treatment of pernicious anemia with a fair degree of efficiency Later Gansslen (*160*) and Castle and Taylor (*161*) demonstrated that a concentrated liver extract could be given intramuscularly and intravenously with a much higher degree of therapeutic efficiency

In the meantime attempts were being made to isolate the active principle in liver and to determine its relationship to the antianemic principle or erythrocyte maturing factor (E M F) supposedly formed by the interaction of the extrinsic and intrinsic factors in the gastrointestinal tract

As previously stated in 1928 Cohn and his collaborators (*51*) isolated a relative crude non protein product which they designated as Fraction G They reported that the active principle did not precipitate with the proteins of liver when they were removed by heat or by acidification to a pH of 5 It was found that the active principle was soluble in 70 per

cent alcohol but was precipitated by 90 per cent alcohol The therapeutically active water soluble yellow powder Fraction G, when subjected to additional steps of purification had some of the characteristics which suggested to Cohn that it was a nitrogenous base Dakin Ungley and West (*162 163*) regarded the active principle as a peptide and considered that in some respects it resembled an albuminose Karrer, Frei, and Fritzsche (*164*) stated that in their opinion the substance was a biuret negative peptide

It was known to be absorbed on charcoal from which it could be eluted with alcohol or phenol In 1937 Jacobson and Subbarow (*165*) put forward their idea that the active principle was not a single compound but a combination of several substances but West in a discussion of this statement by Jacobson and Subbarow (*166*), disagreed with this conclusion Further work bearing on the nature of the active principle was published by Karrer and his associates (*164*) and by Edros (*167*) The electrophoretic pattern of hematopoietic liver extract was examined by West and Moore (*168*) who expressed the hope that further studies might show a correlation between clinical activity and the nitrogen content specific rotation and the amount of the slow component

Until 1947 however the actual nature of the antipernicious anemia principle and its mode of formation remained obscure At this time the initial highly important studies of Shorb (*169 170*) on vitamin B_{12} were instituted followed by those of Rickes and his associates (*171*) at the Merck Research Laboratory in 1948 and the demonstration of the therapeutic effectiveness of vitamin B_{12} in pernicious anemia by West (*172*) introduced a new and productive era in this field of research

Also in 1948 E Lester Smith working independently in England at the Glaxo Laboratories by means of a completely different method partition chromotography isolated two red crystalline substances from beef liver which proved to be identical with the vitamin B_{12} found by the American workers For further details of the historical development of our knowledge in this field consult page 243

Studies beginning in 1947 indicated strongly that the active principle of liver and liver extract and the erythrocyte maturing factor were one and the same substance Further information in support of the belief that vitamin B_{12} is identical with the active principle of liver extract and also the extrinsic factor is found in the work of Berk and his co workers (*173*), confirmed by Hall *et al* (*174*) who showed that this vitamin could serve as the extrinsic factor when given orally with normal human gastric juice to humans Furthermore the administration of extracts of beef muscle when given intravenously are active hematopoietically, as demonstrated by Castle and his associates (*175 176*) and confirmed by Morgan Hall and Campbell (*177*) This lends further support to the belief that the extrinsic factor and the antipernicious anemia principle are closely related if not identical

The Physical and Chemical Properties of Vitamin B_1 —Vitamin B_1 is a *crystalline compound containing 4 5 per cent of cobalt which gives* a reddish purple color and supports the growth of L lactis Dorner The substance also contains phosphorus ■ soluble in water in nearly an hydrous alcohol in acetone containing a small amount of water and it resists 15 minutes of autoclaving at 120 degree (C) but it may be inactivated at room temperature with alkali or acid It has a molecular weight estimated to be between 1300 and 1750 (*178 179*) Other characteristics are as follows it is a levorotatory poly acidic base that has absorption maxima at 2780 3610 and 5500 A The following for mulas have been suggested

$$C_6\,H_{86-90}N_{14}O_{13}PCo$$
$$C_{61}H_{83-0}\,N_{14}O_{13}PCo$$

According to Smith (*95*) the latest advance in the chemical compo sition of vitamin B_1 has been made by Todd and his associates at Cambridge England They have isolated a large portion of the molecule made up of 5 6-dimethylbenzimmazole in glycoside linkage with a mole cule of ribose phosphorylated at C_2 or C_3 The cobalt containing part ■ attached to this phosphorus atom This large portion represents about two thirds of the molecule and its structure is not known at present In addition two molecules of amino proponal and ammonia are attached at some unknown point

Rickes and his associates (*171*) found in 1948 that a product later identified as vitamin B_1 could be isolated from culture broths of a grisein producing strain of Streptomyces gresius and that this was therapeutically *active in the treatment of pernicious anemia They con* cluded that the red crystals derived from this source and vitamin B_1 were identical This discovery has led to a new and important com mercial source of the product

A study of distribution of vitamin B_1 has shown that it is present in diminishing amounts in descending order in the following (*169*) refined liver extracts other liver fractions brewer s yeast skimmed milk peptonized milk and autolyzed yeast cow manure fish meal pancreatin egg white and egg yolk There was little or no activity in crude casein various casein products and digest yeast nucleic acid the alcoholic extract of whey soybean oil meal gelatin and zein It has been found by Lewis and his associates (*180 181*) by the rat assay method that beef kidney contains as much of the vitamin as beef liver two yeast autolysates were negative as was 2 0 grams of thymidine These same workers found that beef and horse meat contain considerable amounts whereas pork was variable

Relation of Vitamin B_1 to the Synthesis of Nucleic Acid —It has been shown that folic acid and vitamin B_{12} are concerned with the chemical reactions which result in the formation of nucleic acid in the cells of the

body. This has been demonstrated by metabolic studies on bacteria, animals and humans (*182, 183, 184, 185, 186, 187, 188*). As emphasized by Jukes, Broquist, and Stokstad (*189*) there is evidence to suggest that folic acid is necessary for the formation of various purines and pyrimidines, as thymine, for endogenous sources of carbon and amino nitrogen and the conversion of these substances or their ribosides. The function of vitamin B_{12} differs somewhat as it appears to be concerned with the formation of ribosides, such as thymidine, from purines and pyrimidines. As stated by Horrigan, Jerrold and Vilter (*190*), "*Folic acid and vitamin B_{12}, therefore, appear to be active at different stages of a chemical chain reaction which leads to the formation of nucleic acids.*" This aspect of the control of nucleic acid metabolism is discussed at length by Strauss in his comprehensive review of vitamin B_{12} (*191*).

By an ingenious method of studying the effects of the direct action of folic acid and vitamin B_{12} by instilling these substances into the bone marrow of patients with pernicious anemia in relapse, it has been concluded by Horrigan, Jerrold and Vilter (*190*) that (1) vitamin B_{12} need not be acted upon by the stomach or liver to be utilized locally by the bone marrow cells and correct a qualitative abnormality in cellular ribonucleic acid, and (2) *folic acid is not utilized locally by bone marrow* within 48 hours after it is instilled within the marrow, but when given orally or parenterally it has the same cytologic and cytochemical effects as vitamin B_{12}. These investigators conclude, therefore, that folic acid must be converted to an active hematopoietic substance by enzyme activity in the body.

If these conclusions are correct, then it is logical to assume that in the presence of a deficiency of vitamin B_{12} and folic acid there will be impairment in the formation of nucleic acid. Furthermore, when this occurs, it is probable that nucleoprotein metabolism likewise is affected and maturation of the red blood cells in the bone marrow is slowed because of disturbed metabolic reactions in the nucleus of the cells. The possibility must also be considered that a deficiency of both vitamin B_{12} and folic acid occurs ultimately in patients with pernicious anemia, although initially there is only a deficiency in vitamin B_{12} absorption due to a deficiency of the intrinsic factor in the stomach.

Our knowledge concerning the relationship of folic acid and vitamin B_{12} to hematopoiesis is still incomplete and any present day theories relating to their actions must be considered as purely tentative and subject to revision as additional information is made available. Evidence suggests that both vitamin B_{12} and folic acid are related biochemically to the process of methylation (*192, 193*) and to nucleic acid synthesis (*194, 195*).

In 1948 Sauberlich and Baumann (*196*) identified a substance in liver extract which was necessary to the growth of certain organisms. This

substance was designated the citrovorum factor It was found that this factor could be replaced by large amounts of folic acid but vitamin B_{12} was ineffective in this capacity Additional studies showed that when rats were fed folic acid there was an increased excretion of the citrovorum factor Hence it was deduced that probably it was formed from folic acid and was a closely related substance Studies demonstrated that it could reverse the action of folic acid antagonists and hence it was concluded that this factor or folinic acid as it has subsequently been called may be the active form of folic acid

Recently Swendseid and her associates (*197*) have found that folinic acid vitamins are present in the livers of mice as folinic acid conjugate and the suggestion is made that folinic acid may be a homologue which is important in the metabolism of animal tissue It is of interest to note that folinic acid appears to be distributed in the particulate and supernatant fractions of the cells in liver tissue whereas vitamin B_{12} is concentrated in the mitochondria

Admirable and comprehensive reviews dealing with all aspects of vitamin B_{12} have been published by Strauss (*191*) Jukes (*191A*) and Girdwood (*198*) An annotated bibliography relative to vitamin B_{12} has been prepared by Merck and Company Manufacturing Chemists Rahway New Jersey 1950

Studies on "Apoerythein" "Erythrotin and Erythein —In a recent study Ternberg and Eakin (*199*) claim to have demonstrated that normal gastric juice contains a heat labile protein fraction which they designate as apoerythrein This substance is presumably identical with the intrinsic factor of Castle and it combines with vitamin B_{12} (erythrotin) to form a vitamin protein complex (erythein) which is resistant to gastric digestion In this combination it is not available to micro organism but is released by heat as such and is again microbiologically active

It has subsequently been claimed (*200*) that apoerythein (intrinsic factor) is present in the saliva of both normal persons and patients with pernicious anemia It is also believed (*201*) that the gastric juice of patients with pernicious anemia contains a principle which inactivates apoerythein (the intrinsic factor) unless the gastric juice is first treated with hydrochloric acid According to Beerstecher and Altgelt (*200*) it appears that the primary defect in pernicious anemia is the achlorhydria which prevents the conversion of the apoerythein or intrinsic factor destroying principle in gastric juice to an inactive and heat resistant form which is resistant to bacteria

Assuming that the intrinsic factor is apoerythein and the extrinsic factor the same as B_{12} or erythrotin then the following statement could be made concerning the theory proposed *Normally* the intrinsic factor is secreted by the saliva which is carried to the stomach but is not destroyed by the intrinsic factor destroying principle This is because the latter is inactivated by free hydrochloric acid The intrinsic factor there

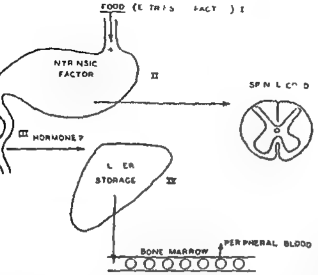

Fig 23 —This chart indicates roughly the normal control mechanism of erythrocyte formation and 4 and possibly 5 explanations of the development of a macrocytic anemia Normally the growth or maturation of the red blood cells in the bone marrow is thought to be controlled by the following processes (1) The extrinsic factor of Castle now thought to be vitamin B 12 is ingested in the food especially with the protein element of the diet (2) This is acted upon by the intrinsic factor which is probably an enzyme secreted by the gastric glands its exact mode of action is unknown (3) When vitamin B 12 is absorbed in the blood stream it is undoubtedly identical with what had been previously designated as the erythrocyte maturing factor or E M F This is absorbed from the intestine and stored (4) in the liver where it is normally released in an orderly fashion to control maturation of the erythrocytes in the bone marrow largely through participation in the metabolism of the nucleus of the immature red blood cells In pernicious anemia this normal process is interrupted as the result of an inadequate amount of intrinsic factor in the gastric secretions and consequently a maturation arrest of the erythrocytes occurs in the bone marrow a diminished number of red blood cells are released to the circulating blood and hence an anemia develops In a dietary deficiency ("extrinsic macrocytic anemia) the same final result is produced by lack of extrinsic factor in the diet It is known also that both the extrinsic and intrinsic factors may be present in normal amounts but a macrocytic anemia may develop either because of an inadequate intestinal absorption of the E M F (seen in intestinal anastomoses and strictures) or on account of widespread liver disease due to imperfect storage in the liver and failure of proper release of the E M F to control normal maturation of the erythrocytes in the bone marrow And finally it must be considered that with the normal formation absorption and storage of the E M F a macrocytic anemia may develop because for unknown reasons the marrow may not react normally to the E M F (the acrestic anemia of Wilkinson) *It should be kept in mind however that while vitamin B 12 plays an important role in the normal maturation of the erythrocytes other factors such as folic acid are also vitally concerned in this process* (See page 261)

fore combines with vitamin B_1 to form a stable substance which is resistant to bacteria carried to the intestine and absorbed where it eventually participates in the normal control of the maturation of the red blood cells

In patients with pernicious anemia however there is no hydrochloric acid in the gastric secretion Hence the intrinsic factor destroying principle is not inactivated It is free therefore to destroy the intrinsic factor which reaches the stomach from the saliva Consequently there is a deficiency of intrinsic factor to react with extrinsic factor B_1 and therefore the erythrocyte maturing factor which controls the maturation of the red blood cells is not present in a normal amount

This theory which brings new information to light is difficult to accept in toto at present for several reasons First because many persons have an achlorhydria for years without developing pernicious anemia second the administration of hydrochloric acid is of no value in the treatment of the disorder and third it is difficult to understand how the picture of pernicious anemia might develop in patients in whom a total gastrectomy had been performed Nevertheless the theory is an ingenious one supported by new and reliable data which should be given consideration but await further amplification and confirmation

Recently Beerstecher (201) has claimed that evidence has been produced which indicates that the intrinsic factor combines with vitamin B_{12} to produce a complex the erythrotin of Eakin and Fernberg which is normally enzymatically degraded to form the active principle thus explaining the inability of vitamin B_{12} synthesized in the gut to manifest a hematopoietic response

SUMMARY AND TENTATIVE THEORY OF THE ETIOLOGY OF PERNICIOUS ANEMIA AND OTHER MACROCYTIC ANEMIAS WITH A MEGALOBLASTIC BONE MARROW

1 Normally a sufficient amount of *vitamin B_{12}* now regarded as the *extrinsic factor* is present in the diet especially in glandular meats muscle tissue eggs and milk (plant materials show no measurable amount) This upon ingestion and being taken into the stomach is acted upon by the *intrinsic factor*

2 The *intrinsic factor* is an enzyme normally secreted by the glands of the gastric mucosa from all parts of the stomach but possibly only in small amounts from the pyloric region Apparently its sole function is to make vitamin B_{12} absorbable Upon absorption it acts to form nucleic acids which in turn are converted to nucleoproteins These are essential to the development of the nuclei of the young red blood cells and hence control their normal rate of maturation After vitamin B_{12} has been absorbed it is probably what has heretofore been designated the *erythrocyte maturing factor* or the active hematopoietic principle of liver

3 *Pteroylglutamic acid* (*folic acid*) is ingested in the food largely in vegetables as an inactive conjugate which is acted upon in the body by an enzyme which liberates the active form It then participates in the formation of nucleic acids from purines and pyrimidines and thereby contributes to the normal metabolism of the nucleus and like vitamin B_{12} promotes the normal rate of maturation of the red blood cells in the bone marrow It is assumed therefore that both vitamin B_{12} and folic acid are concerned normally with the formation of nucleic acid and hence directly in the rate of normal maturation or development of the red blood cells in the bone marrow

4. In pernicious anemia there is a diminished or absent amount of intrinsic factor in the stomach due to failure of the stomach glands to function normally. Consequently the amount of vitamin B_{12} which is available becomes less until a vitamin B_{12} deficiency is created. To compensate for this and prevent the development of an anemia a larger proportion of nucleic acid synthesis is taken over by folic acid and consequently a folic acid deficiency is ultimately also created. Hence in a patient with pernicious anemia in relapse there is eventually both a vitamin B_{12} and folic acid deficiency. It is to be anticipated therefore

Fig. 24.—Roentgenogram of a patient with linitis plastica in whom the gastric secretions did not contain the intrinsic factor and an anemia resembling pernicious anemia was present. The anemia responded readily to desiccated stomach therapy. (Goldhamer, courtesy *American Journal of Medical Sciences*.)

that such a patient will respond to either B_{12} or folic acid. In most instances when vitamin B_{12} is administered the patient's appetite increases to such an extent that an increased amount of food containing folic acid will be available. In some patients however in whom the appetite is poor a folic acid deficiency may persist and the blood will not return *entirely* to normal until this material is given.

In patients with the macrocytic anemia of pregnancy vitamin B_{12} is therapeutically inactive whereas folic acid is curative. Here possibly due to increased demands of the fetus, poor diet or other unknown factors a folic acid deficiency may develop initially and additional demands of nucleic acid metabolism be placed upon vitamin B_{12}. During pregnancy there is possibly not sufficient time for a vitamin B_{12} deficiency to develop and hence the administration of this vitamin is ineffective but as

there is a folic acid deficiency one would expect that the therapeutic use of this material would cause a remission in the blood disorder which it does

Attempts to Produce Pernicious Anemia Experimentally—Despite many experiments on animals in an attempt to produce this form of anemia experimentally, *in no instance has the effect been entirely successful* although macrocytic anemias of various types have resulted from some of the procedures instituted To claim that true addisonian pernicious anemia has been produced experimentally one must have been responsible for the appearance in an animal of the following 1 a macrocytic anemia with leukopenia thrombopenia and a megaloblastic

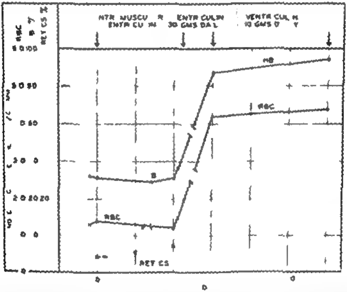

Fig 25—Showing the response of a macrocytic anemia in a patient with cancer of the stomach to ventriculin orally after a preliminary reticulocyte rise following the injection of an experimental preparation of ventriculin This patient had linitis plastica as indicated by the typical roentgen ray picture The intrinsic factor in the gastric secretions was demonstrated to be absent by incubating the patient's gastric juice with beefsteak and administering it to a patient with known pernicious anemia It failed to produce a reticulocyte response (Sturgis and Goldhamer courtesy *Annals of Internal Medicine*)

bone marrow 2 an anemia which responds with a reticulocyte rise and a prompt increase of the hemoglobin and red blood cell count to normal as the result of treatment with liver extract vitamin B_{12} or folic acid 3 glossitis with typical changes in the tongue 4 characteristic degenerative changes in the peripheral nerves and the posterior and lateral columns of the spinal cord and 5 a histamine resistant achlorhydria Never has such experimental state with the above five criteria been produced in animals

4 In pernicious anemia there is a diminished or absent amount of intrinsic factor in the stomach due to failure of the stomach glands to function normally Consequently the amount of vitamin B_{12} which is available becomes less until a vitamin B_{12} deficiency is created To compensate for this and prevent the development of an anemia a larger proportion of nucleic acid synthesis is taken over by folic acid and consequently a folic acid deficiency is ultimately also created Hence, in a patient with pernicious anemia in relapse there is eventually both a vitamin B_{12} and folic acid deficiency It is to be anticipated therefore

Fig 24 —Roentgenogram of a patient with linitis plastica in whom the gastric secretions did not contain the intrinsic factor and an anemia resembling pernicious anemia was present The anemia responded readily to desiccated stomach therapy (Goldhamer courtesy *American Journal of Medical Sciences*)

that such a patient will respond to either B_{12} or folic acid In most instances when vitamin B_{12} is administered the patient s appetite increases to such an extent that an increased amount of food containing folic acid will be available In some patients however in whom the appetite is poor a folic acid deficiency may persist and the blood will not return *entirely* to normal until this material is given

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in dogs swine, monkeys or rats has been followed by the appearance of typical pernicious anemia namely a hyperchromic megalocytic anemia hyperplasia of the bone marrow and the capacity to react favorably to liver extract In the opinion of these authors the failure to produce pernicious anemia experimentally in animals may be due to 1 non existence of this type of anemia in animals 2 production of the intrinsic factor by the duodenum and perhaps other parts of the gastro intestinal tract or 3 the possibility that a disturbance of some unknown factor or factors is required in addition to gastrectomy and duodenal resection

The experiments of Geiger Goodman and Claiborn (204) are of importance from the standpoint of indicating that the liver has a significant function in storing the erythrocyte maturing factor and also that the active principle is related to the digestive action of the stomach They removed the stomachs from swine and at monthly intervals killed the animals and assayed the potency of the livers by administering extracts prepared from them to patients with pernicious anemia It was found that after total gastrectomy in the hog the liver becomes depleted of antianemia potency which is detectable after the first month and is complete at the sixth month In another experiment they severed the continuity of the stomach from the gastrointestinal tract at both the cardiac and pyloric ends but kept the nerve and blood supply intact Under such conditions the interaction between the extrinsic food factor and the intrinsic factor of the gastric juice would be disturbed as food could not enter the stomach Theoretically the erythrocyte maturing factor could not be formed under these circumstances and the liver would therefore lose its antipernicious anemia properties The animal in which this operation had been carried out was killed in the eighth post operative month and the liver found to be devoid of all antipernicious anemia activity when given to two patients with the disease From this experiment it would appear that the digestive role of the stomach is essential to the formation of the erythrocyte maturing factor therefore and their findings are in accord with the theory of Castle

The literature dealing with the clinical association of *macrocytic anemia with intestinal stricture and anastomosis* has been reviewed by Cameron Watson and Witts (205) who concluded that the anemia is probably due to stagnation of intestinal contents and the absorption of toxic products They suggested and later carried out (206) their idea that the experimental production of blind loops in the small intestine of rats offered a promising approach to the study of the macrocytic anemias They considered that success followed their experimental operations on the small intestine in rats with the creation of such blind loops or intestinal stenosis The anemia thus created did not usually develop until an interval of several weeks or months following the operation It was

In general two different experimental approaches have been employed in an attempt to reproduce the features of the disease There have been (1) various types of operations on the gastro intestinal tract and (2) alterations in the diet calculated to create a deficiency in folic acid or vitamin B_{12} or both

Of the *operations carried out in the gastro intestinal tract,* two appear to be the logical approach for the production of such an anemia because they have been known to result in a macrocytic anemia in humans They are total gastrectomy and the production of various types of anastomoses and stenoses in the intestines For further details of the clinical aspects of macrocytic anemias due to such causes in man consult page 352

Ivy (*202*) in reviewing his studies on the effect of gastrectomy in various animals states that *all* attempts to reproduce the blood and bone

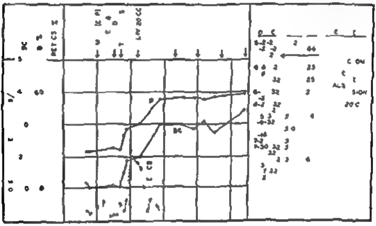

Fig 26 —Showing the development of a macrocytic anemia which responded to antipernicious anemia therapy in a woman age 29 years who had a partial gastrectomy performed for a gumma of the stomach The anemia developed within two years after the operation (Goldhamer courtesy *Annals of Internal Medicine*)

marrow changes of pernicious anemia in animals by gastrectomy and dietary modifications have met with failure Furthermore he has no faith in the reports to the contrary which appear in the literature He concludes that total gastrectomy does not cause pernicious anemia combined degeneration of the spinal cord stomatitis and glossitis in the rat (after one year) dog (after 12 years) pig (after three years) or monkey (after three years) Nor does evidence of pernicious anemia develop in gastrectomized monkeys during an interval of 152 days when fed a diet patterned after that of Mohammedan women in Bombay who frequently *have a macrocytic anemia*

In a very comprehensible article dealing with the subject, in which there is an admirable summary of the literature Petri and Jensenius (203) express an opinion which is in complete accord with that of Ivy They conclude that neither total gastrectomy or partial resection of the stomach

For further references dealing with the attempts to produce a macrocytic anemia in animals by experimental means the extensive bibliography in the article by Cartwright and his associates should be consulted (208)

The Role of Increased Hemolysis in the Production of the Anemia — The arguments favoring the importance of abnormal hemolysis in the production of the anemia have been summarized by Dock (213) and by Bloomfield (214) Although the view that there is an increased destruction of the erythrocytes in patients with pernicious anemia has been relegated to the background in recent years it must be admitted that there is still strong suggestive evidence which indicates that this process may be of importance in the production of the anemia although it is probably secondary to decreased blood formation It must be admitted that those findings which are ordinarily identified with the hemolytic anemias are also found in pernicious anemia These are an increase in the amount of the blood bilirubin an increased excretion of the bile pigments in the stool and urine and a high iron content of the blood serum liver kidney and spleen As pointed out by Dock (213) and Dobriner and Rhoads (215) the bone marrow picture in pernicious anemia resembles closely that observed in certain anemias such as hemolytic icterus experimental hemorrhagic anemia and saponin anemia which are not caused by bone marrow defects If coproporphyrin I excretion is accepted as an index of bone marrow activity some account must be taken of the fact that it is increased in relapses of pernicious anemia and is decreased appreciably when liver therapy is instituted just as it does in hemolytic icterus following splenectomy

Evidence is accumulating which is interpreted by Johnson Freeman and Lognini (216) as indicating that liver extract acts generally in the anemias by protecting the erythrocytes against hemolysis It has been shown by Paschkis and Taylor (217) that liver will protect red blood cells against saponin hemolysis and also that it will control an anemia produced in dogs by indole and a deficient diet Although it is not known absolutely that this anemia is hemolytic in nature it is recognized that indole will cause increased erythrocyte destruction

Recently Johnson *et al* (216) have shown that the erythrocytes of normal man are rendered more susceptible to hypotonic hemolysis in the standard fragility test by exposure to lipemic serum They conclude that fat ingestion may be one factor in the normal daily destruction of red blood cells Their studies in patients with untreated pernicious anemia showed that lipemic serum and red cells of the same individual were mixed By contrast when lipemic serum of adequately treated patients with pernicious anemia and normal man were mixed with their own red blood cells only increased fragility but no actual hemolysis was produced They state that their observations suggest the possibility that

macrocytic in type and acute in course Life could be prolonged with refined liver extract vitamin B_{12} or folic acid While these experiments resulted in the production of a macrocytic anemia and shed light on factors which may be important in the production of that disease it cannot be said that the condition produced is typical of true addisonian form of the disease

Experimental Macrocytic Anemia Produced by Dietary Deficiencies — In 1941 Wintrobe (*207*) summarized some early attempts to produce macrocytic anemia by feeding newborn pigs a diet deficient in the extrinsic factor The experiments were productive of an anemia which was somewhat macrocytic and accompanied by hyperplasia of the bone marrow Of great interest were changes observed in the nervous system as they simulated to some extent the neural signs present in pernicious anemia These lesions could be prevented by the addition of yeast or whole liver to the diet

In 1949 Cartwright Tatting Ashenbrucker, and Wintrobe (*208*) reviewed the literature relating to the experimental production of nutritional macrocytic anemia in swine and published observations of their own They produced a deficiency of pteroylglutamic acid in swine by feeding a purified diet containing casein and supplemented with seven of the B vitamins sulfasuxidine and a folic acid antagonist Two types of casein were used in separate groups of animals one containing a significant amount of extrinsic factor activity and a purified casein with little activity They observed in these animals a severe macrocytic anemia leukopenia slight thrombopenia and a hyperplastic bone marrow containing immature nucleated red blood cells which resembled the megaloblasts seen in the marrow of patients with pernicious anemia These changes in the blood were not delayed or prevented by the intra muscular injection of 1 unit of liver extract daily given as 15 units every 15 days The blood and bone marrow however returned rapidly to normal following the administration of folic acid Purified liver extracts and vitamin B_{12} were found to possess some hematopoietic activity in several animals but it was considerably less than that of folic acid These investigators conclude that their results *indicate the necessity of both folic acid and a factor in liver extract similar to or identical with vitamin B_{12} for normal hematopoiesis in swine* A study of a vitamin B_{12} deficient diet in baby pigs plus the administration of a folic acid antagonist led Johnson and his associates (*209*) to the same conclusion namely that both vitamin B_{12} and folic acid are involved in hemato poiesis in swine

Somewhat similar studies have been carried out by Welch Heinle and their associates (*210 211 212*) who conclude that folic acid can cause a complete hematopoietic response in swine in an anemia produced by a purified diet containing only a small amount of extrinsic factor"

integrity of the nervous system That a deficiency of either one of these substances or both or a disturbance in their metabolism may account for the lesions of subacute combined degeneration of the spinal cord must be considered but this possibility remains a matter for additional investigation It is an attractive theory to assume that some deficiency either of the diet or one conditioned by the achlorhydria may cause a decrease in a nerve protective factor which causes lesions of the peripheral nerves when acting mildly and with an increasing degree of deficiency further changes in the posterior and finally the lateral columns are produced

Etiology of Various Other Changes in the Disease—The cause of the glossitic change has not been demonstrated but at present the most acceptable theory of its pathogenesis is based likewise upon an assumed deficiency of some component of the vitamin B complex as emphasized by Middleton (*219*) The previous view as held by William Hunter that it is an inflammatory change is no longer tenable The most obvious explanation is that it might arise as the result of an actual dietary deficiency of some component of the vitamin B complex or from an impaired absorption of it due to the achlorhydria One point which has not been explained by any theory yet proposed is why the glossitis should show spontaneous periods of remission and exacerbation

The premature gray hair of patients with pernicious anemia has never had a satisfactory explanation but it is very tempting to speculate over the possibility that perhaps para amino benzoic acid or panthothenic acid components of the vitamin B complex claimed by some to be related by a deficiency to gray hair may play a role in the production of this change in patients with pernicious anemia Here again these substances might not be reduced in the dietary intake but may fail to be absorbed in normal amounts on account of the achlorhydria

PATHOLOGY

General Findings—Due to the present day effectiveness of antipernicious anemia medication the characteristic pathologic anatomy of the disease is now rarely seen at necropsy This is because patients who are treated rarely die of the anemia of pernicious anemia but succumb to some coincidentally associated disease common to the age group The blood at the time of death is often normal or at least at such a high level that the symptoms of anemia are absent Before 1926 when liver therapy was introduced and death usually came at a time when the anemia was severe the commonly observed findings were as follows the evidences of the anemia widespread fatty degeneration of many parenchymatous viscera and muscles a predominance of megaloblasts in the bone marrow interpreted by a majority of present day pathologists as a maturation arrest of the red blood cell series at the megaloblast stage deposits of

TABLE XV

2000 CASES WITH DIAGNOSIS OF SUBACUTE COMBINED DEGENERATION OF THE SPINAL CORD AT MAYO CLINIC

77 or 3 5% had free HCL in gastric secretions
69 of the above cases *were not true* S C D (*Arteriosclerosis Trauma Multiple Sclerosis Infection Myelitis or Syphilis*)
8 cases (0 4% of the 2000 cases) presented the true picture of S C D with free HCL
5 of these suffered from nutritional disturbances
3 had no evidence of the nutritional factor in etiology

TABLE XV—The facts stated in the above table indicate that practically all patients with subacute combined degeneration of the spinal cord either have an achlorhydria which may account for malabsorption of some article from the diet or they suffer from nutritional disturbances The only exceptions in these 2000 cases are three patients who did not have an achlorhydria and were also free from evidences of nutritional disturbances
(Woltman and Heck Courtesy *Archives of Internal Medicine*)

an excessive destruction of erythrocytes by the digestive products of fat is one of the etiologic factors in pernicious anemia because the red blood cells of such patients have an abnormal sensitivity to such products They also considered that a deficient plasma protection against these materials may be involved

Etiology of the Neurological Manifestations—Although the work of Castle and his collaborators have shed considerable light on the cause of the anemia of pernicious anemia the factors responsible for the degenerative changes in the nervous system still remain obscure What ever may be the cause it must differ fundamentally from that of the anemia because there is no constant relationship between the existence of the two in patients It is recognized for example that there may be *extensive spinal cord changes with a very slight or no anemia or a* pronounced anemia with insignificant changes in the nervous system Yet the two must have *some* factor in common because of their frequent association

The most acceptable view at present is that the lesions in the nervous system result from the deficiency of some particular substance in the diet or the malabsorption of it as the result of the constantly present achlorhydria There is no conclusive evidence as to just what this hypothetical constituent of the diet may be but it is most commonly considered to be one of the components of the vitamin B complex Interesting data concerning 2000 cases of subacute combined degeneration of the cord are presented in Table XV *In Table XVI are listed the* conditions in which this neurological syndrome may appear almost all are associated with a nutritional disturbance It is of possible interest in relation to the neural changes of pernicious anemia that sensory neuron degeneration can be produced in pigs involving the peripheral nerves the posterior roots and the posterior funiculi of the spinal cord by means of a diet deficient in calcium pantothenate or pyridoxine (218) It is thought that these two substances are essential for maintaining the

were extensive and severe with a thinning of the mucosa to about one half that of the pyloric zone This thinness was due to a completely abnormal type of mucosa in which the parietal and chief cells the normal cell types were absent According to this investigator the mucosal glands were shorter less numerous and more tortuous than those found normally in the fundic region

He considers that the gastric changes in cases of pernicious anemia are sufficiently alike to be considered as a group Changes of so-called "chronic gastritis" have a superficial resemblance to those occurring in pernicious anemia but such alterations are limited almost exclusively to the region of the pylorus The lesions of pernicious anemia in the stomach must be considered as different from those occurring in other diseases of old age The changes reported by Cox were absent in the stomach of one patient with sprue who had a long standing fatal macrocytic anemia

Additional studies of the gastric mucosa in patients with pernicious anemia have been made by Olson and Heck *(221)* A total of 94 cases of pernicious anemia was investigated which comprised the total number which came to necropsy at the Mayo Clinic between the years 1911 to 1942 Tissues were available in only 41 of these cases The gastric mucosa of patients dying of pernicious anemia differed from those of patients of a control group in the following particulars (1) the mucosal layer was thinner (2) atrophy of the specialized cells was almost complete (3) there were fewer glandular tubules and (4) hyperplasia of the mucous glands was extremely common Actual measurement of the thickness of the mucosal layer gave the following results in routine cases 0 98 millimeter in untreated pernicious anemia 0 85 millimeter The hyperplasia of the mucous glands which was present in about 85 per cent of the cases of pernicious anemia varied from minor changes to an arrangement which was indistinguishable from carcinoma There was an increase in the number of cases of both polyps and carcinoma of the stomach in patients with pernicious anemia who had received treatment Two of the 63 untreated patients had carcinoma of the stomach whereas in 31 cases who had received treatment it was present in six The incidence of benign polyps was also increased in the treated group Polyps were found in three of the 63 cases in which treatment had not been given and in eight of the 31 cases in which treatment had been given That there should be an increase in the number of cases of pernicious anemia who develop polyps and carcinoma of the stomach with treatment is to be expected This is because the processes which are active in producing the changes in the gastric mucosa are permitted by an extension of life to act for a much longer time than prior to the modern treatment of pernicious anemia

The cause of the stomach lesion is not apparent and any suggestion concerning this phase of the etiology must at this time be purely specula

TABLE XVI

THE SYNDROME OF SUBACUTE COMBINED DEGENERATION OF THE SPINAL CORD MAY BE ASSOCIATED WITH THE FOLLOWING CONDITIONS

1 Pernicious Anemia	6 Obstruction or Fistulae Intestinal Tract
2 Pre Pernicious Anemia	7 Hemolytic Jaundice
3 Scurvy	8 Amyothrophic Lateral Sclerosis
4 Pellagra	9 Sprue
5 Pancreatitis	10 Chronic Alcoholism

TABLE XVI —This list of conditions which may be associated with the syndrome of subacute combined degeneration of the cord all have an associated disturbance in nutrition It furnishes further evidence to indicate that such a change in the nervous system is due to a nutritional defect which may be either the lack of some article of diet or the inability to absorb or utilize it
(Woltman and Heck Courtesy *Archives of Internal Medicine*)

hemosiderin an iron containing pigment derived from hemoglobin in the liver kidneys, and spleen degenerative changes in the peripheral nerves and similar alterations in the posterior and lateral columns of the spinal cord The changes in the stomach consisting largely of atrophy of the mucosa in the fundic zone is now thought to be constantly present and is perhaps the most distinctive finding of the disease from the standpoint of the pathologist It is discussed in more detail below Hence, unless the changes in the stomach are established as a specific lesion there is no single pathologic finding which is recognized as peculiar to pernicious anemia exclusively The pathologist arrives at the anatomical diagnosis by excluding other causes of anemia and by the presence of the changes enumerated above

Brown (*220*) reported that at necropsy benign gastric tumors were found in [illegible] per cent of patients with the disease and cholecystitis and cholelithiasis were observed in about 16 per cent of a group of 151 patients

Patients dying during a hematologic remission show only the stomach changes neurologic lesions involving the peripheral nerves the spinal cord and sometimes the brain and atrophy of the mucosa of the tongue Also there may be present evidences of the infection of the urinary tract and the associated or complicating disease which was the immediate cause of death

Changes in the Stomach —The changes in the stomach in patients with pernicious anemia are of paramount importance because the most generally accepted theory of the disease at present places the seat of the disorder in this viscus Cox (*130*) summarizes his own investigations in regard to the alterations of the stomach in patients with this disease and gives a review of the recent literature in this field He found that the most striking change was a pronounced alteration in the mucosa of the fundus and the body which was in contrast to the relative freedom from abnormalities of the pyloric region *In the fundic area the changes*

Sternal marrow aspiration during relapse as is to be expected shows an increase in the number of nucleated red cells with about 20 to 30 per cent megaloblasts There is a definite absence of mature and moderately mature erythropoiesis Frequent foci of granulopoiesis are observed composed almost entirely of myelocytes metamyelocytes and mature polymorphonuclear cells There is usually a striking decrease in megakaryocytes

Pathologic Changes in the Nervous System—The initial lesion is a swelling of the myelin sheaths localized to a small area of white matter which progresses to outspoken fatty degeneration The degenerative changes are not systemic in nature as they do not affect the long fiber tracts in the posterior and lateral columns uniformly throughout their length The disease process begins with foci scattered throughout the

Fig 27—Cross section of the spinal cord in the lumbar region of a patient with pernicious anemia showing advanced degenerative changes in the posterior and lateral columns This patient had loss of sense of motion and position and an absence of the vibratory sense in the lower extremities and a moderately advanced spastic paraplegia × 30 (Weil and Davison courtesy *Archives of Neurology and Psychiatry*)

posterior and lateral columns of the lower thoracic portion of the cord and gradually spreads upward and downward The most acceptable present day view is that the primary involvement is of the myelin sheaths the destruction of which produces secondary swelling and fragmentation of the axis cylinders This is in no sense an inflammatory reaction and there is no spontaneous attempt to repair the lesion by the organizing function of the fibrous glial cells There is no dense glial scar formation and hence the term combined sclerosis is a misnomer and should be abandoned Davison (228) claims however that with liver therapy there is glial proliferation which replaces the destroyed tissue

Recently Adams and Kubik (229) have emphasized the occurrence of lesions of the white matter of the brain in patients with pernicious anemia and have reviewed the literature dealing with that subject They emphasize that the important pathological changes consist of a diffuse but uneven degeneration of nerve fibers in the spinal cord and cerebral white matter with relatively little proliferation of fibrous glia According to

tive There does not seem to be any relation between them and an inflammatory change such as chronic gastritis Nor can it be said that the gastric mucosa lesions are due to the anemia because the achlorhydria precedes rather than follows it It is generally agreed that hereditary influences must be important and it is assumed that in some unknown manner the individual who develops pernicious anemia inherits a portion of the gastric mucosa which is especially vulnerable to some unknown influence At the present stage of our knowledge it is not possible even to speculate as to what the immediate precipitating cause of the condition may be

Gastroscopic Observations of the Gastric Mucosa in Patients with Pernicious Anemia —It seems to be fairly well established (*222, 223 224, 225*) from gastroscopic examination that chronic gastritis usually of the atrophic type is not infrequently associated with the pernicious variety and sometimes other forms of anemia It is known that it frequently precedes the changes in the blood in pernicious anemia but it is not possible to establish a definite relationship between it and this variety of anemia There is some evidence that the gastric mucosa shows improvement following treatment as noted through the gastroscope but this does not indicate that it has returned to normal and that the glands of the mucosa can again function normally

Atrophy of the gastric mucosa as determined by gastroscopic observation occurred in only 59 per cent of the 100 patients with pernicious anemia studied by Hardt Schwartz and Steigmann (*226*) This change could not be correlated with the length of time the disease had been present the amount of previous liver therapy, or the existing blood picture In some cases they observed patchy and in others diffuse changes in the gastric mucosa Only nine of 47 patients showed improvement in the gastric mucosa following therapy

The Bone Marrow —A constant change in the bone marrow of patients with pernicious anemia in relapse is the increase in the number of nucleated red blood cells from the average normal of approximately 20 per cent or less to 35 or 50 per cent of all nucleated cells The most characteristic finding is the presence of megaloblasts which make up from 20 to 30 per cent of all marrow cells Such a megaloblastic marrow is observed in pernicious anemia achrestic anemia and certain nutritional anemias such as sprue In practically all other varieties of anemia the predominating cell in the marrow is the normoblast

Peabody (*227*) by means of biopsies observed that during relapse the essential histologic lesion is a proliferation of megaloblasts which produced a hyperplastic but functionally inefficient marrow as cell development beyond this stage does not proceed at a normal rate In other words there was a maturation arrest During a remission there is a decrease in the number of megaloblasts and a great relative increase in the normoblasts and mature red blood cells in the marrow

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these observers the lesions in the brain and spinal cord resemble each other so closely that there can be no mistake concerning their identity An analysis of their cases and others indicates that patients with brain lesions have mental symptoms but that the converse of this statement is not necessarily true since anatomical cerebral changes are not always found in cases in which mental symptoms have been present

Although relatively little attention has been paid to the alterations in the peripheral nerves, Hamilton and Nixon (38) made the important observation that degenerative changes are present, similar to those observed in the spinal cord These findings have been confirmed by the more recent work of others (230 231)

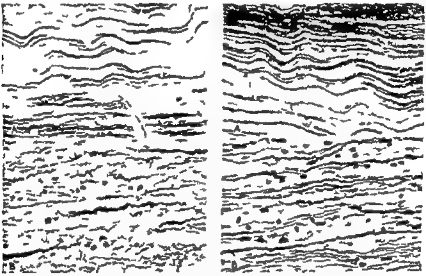

Fig 28—A in the upper left hand corner shows a longitudinal section through the posterior columns of the spinal cord of a patient with pernicious anemia who received inadequate liver therapy There is some destruction of the myelin sheaths while others appear to be well preserved Compare this with A in the upper right hand corner which is a longitudinal section through the involved posterior columns of the cord of an adequately treated patient in which there is only moderate destruction of the sheaths Myelin sheath stain with magnification × 154 in both sections B in the lower left hand corner shows destruction of axis cylinders fragmentation swelling and corkscrew appearance in the posterior columns of the cord of a patient who was inadequately treated with liver Compare this with B in the lower right hand corner which shows a longitudinal section through the posterior column of the cord from a patient who had been adequately treated there is preservation of the axis cylinders except for occasional swelling Bielschowsky stain × 308 (Davison courtesy *Archives of Internal Medicine*)

SYMPTOMS

General Description —The complaints of a patient with pernicious anemia may be conveniently divided into four main groups namely (1) those referable to the anemia (2) the gastro intestinal tract (3) the

nervous and (4) the cardiovascular system In almost all patients there are usually manifestations of varying degree representing each group

The onset of the disease is always insidious and consequently it is often difficult for the patient to state definitely when the earliest complaints appeared In about one third of the cases the initial symptoms are referable to the anemia They consist of ease of fatigue weakness pallor and dizziness Cardiovascular manifestations, which are also due mainly to the anemia are the first evidences of the disease in about 10 per cent of the patients There are dyspnea on exertion palpitation sometimes edema of the ankles and occasionally cardiac pain characteristic of angina pectoris In about one third of the cases the onset is characterized by gastro intestinal complaints such as anorexia nausea vomiting mild epigastric discomfort and either constipation or diarrhea or an alternation of the two The associated gallbladder disease which is present in some patients must be kept in mind as an explanation of some gastro intestinal symptoms Occasionally the sole symptom which attracts the patient's attention to the disease is recurrent attacks of glossitis The onset in about 25 per cent of the patients is with neurological manifestations and of these the most constantly encountered one is persistent numbness and tingling of the hands and feet Other neurologic changes are weakness and spasticity of the muscles of the lower extremities due to involvement of the lateral columns of the spinal cord ataxia resulting from degenerative changes in the posterior columns of the cord and loss of control of the sphincter of the bladder Occasionally muscle tenderness may be present possibly as a result of involvement of the peripheral nerves

The usual history is one of a very gradually developing weakness which becomes progressively worse until the patient is no longer able to continue working Commonly associated with this are gastro intestinal complaints most frequently anorexia When the physician is first consulted the weakness has usually not progressed to the point where it has made bed rest necessary and efforts may still be made by most patients to carry on with difficulty their normal daily activities It is amazing that some patients with low red blood cell counts have had sufficient strength to accomplish as much as they do Coincident with the appearance of weakness and ease of fatigue there is usually a gradually developing pallor which often has a slight yellowish tint when the anemia becomes pronounced About 90 per cent of the patients complain of numbness and tingling of the hands and feet which also may be the earliest manifestation of the disease As the anemia becomes pronounced there may be nausea vomiting extreme weakness fever and delirium

If the disease has existed in the patient for any length of time there is frequently a history that spontaneous improvement has set in and for intervals of several weeks or months there may have been such a gain in

strength that a resumption of an almost normal life has been possible This is typical of a spontaneous remission which almost always occurs in the course of the disease

Special Features of the Patient's History

Pallor with a Yellowish Tint—Almost since the earliest descriptions of the disease it has been emphasized that one of the distinctive signs of the disease is the color of the skin which results from a combination of pallor with a yellow tint This was described as "lemon yellow" or "grapefruit color" *It is rarely so pronounced as to resemble a true jaundice* and is not commonly noticed by the patient unless attention is directed to it by others The basis for this color is the increased amount of bilirubin in the blood which is always present when the red blood cell count is low and in general bears a rough relationship to the severity and duration of the anemia

In recent years, however it is not so common to observe patients with this yellowish color and hence one should *not hesitate to make a diagnosis of pernicious anemia in its absence* The explanation of its decreasing frequency is probably because now one does not see so many patients with an advanced degree of anemia This may be accounted for by the fact *that patients now usually consult a physician earlier in the course of any disease* and with modern diagnostic measures which are at present almost universally available the diagnosis is made before the red blood cell count falls to an extremely low level Furthermore, with the advent of the liver therapy in 1926 we no longer see patients with severe degrees of anemia which persist for long intervals Nevertheless if a patient with a red blood cell count below one million and a half is suspected of having pernicious anemia the absence of a yellowish tint casts some suspicion on the diagnosis *for with this degree of anemia one would expect to observe* an increase in the blood bilirubin to such a degree that a distinct yellowish color to the skin and conjunctivae would be apparent

Glossitis—*Recurrent attacks of sore tongue occur in about two thirds* of all patients with pernicious anemia and when present are highly suggestive, but not specific of the disease It may also occur in idiopathic hypochromic anemia anemia of pregnancy sprue pellagra the Plummer Vinson syndrome malnutrition associated with dysentery and anemia intestinal stricture diphyllobothrium infestation and in patients with achlorhydria due to other conditions It is pointed out by Waldman and Pelner (232) that niacin and riboflavin deficiency are causes of burning of the tongue in patients with avitaminosis The condition may also be associated with smoking irritating food and drink They state that it may be associated with neurogenic and psychogenic causes and refer to an observation by Alvarez (233) that burning of the tongue may be the only symptom of thrombosis of a small intracranial vessel They also state

that this symptom may be associated with the menopause. In their opinion there is a fairly large group of patients with this symptom in whom the cause is thickening of the salivary secretion with resultant dryness of the mouth and concomitant symptoms. This condition may be relieved according to the authors by the administration of prostigmine bromide 7.5 milligrams given three times daily after meals

Glossitis may be the initial manifestation of pernicious anemia but it usually appears after the disease is well developed. The term recurrent is very aptly applied to the condition because it characteristically appears for a period of several weeks and then without apparent reason disappears spontaneously only to recur again after a variable period of one to several weeks or longer. During the exacerbations the tongue is often extremely painful a fiery red and in some instances the discomfort may be so great as to interfere seriously with the ingestion of food. In one patient with whom I am familiar it was necessary for a short time to cocainize the tongue in order to permit eating

The entire dorsum of the tongue is usually involved but sometimes the changes are apparent only in circumscribed areas. Occasionally there may be associated superficial whitish ulcers which resemble those observed in apthous stomatitis. In about one half of the cases there is atrophy of the lingual papillae which commonly progresses to their complete disappearance thus giving the typical picture of the smooth atrophic tongue of the disease. Such atrophy appears in my experience in about 50 per cent of the cases. It is interesting to note that the smooth atrophic appearance may appear with or without a previous history of attacks of sore tongue. Although all patients with the disease do not have glossitis or an atrophic tongue I have never observed a patient with pernicious anemia in relapse in whom the tongue has been unmistakably coated. For some reason unknown to me the tongue is always clean

Paraesthesia of the Extremities—This is a significant symptom of the disease as it is present in approximately 90 per cent of all patients and is therefore of great importance from a diagnostic standpoint. In most patients paraesthesias appear only in the course of the illness but they may be the sole initial complaints for a considerable period of time. It almost without exception involves all four extremities and most commonly is limited to the fingers and toes although frequently it may be present in the entire hand or foot and can even extend to the full length of arm or up the legs to the pelvis or the lower part of the thorax in advanced cases. In untreated patients it may vary from day to day in intensity but it never completely disappears. It may be affected favorably in therapy but usually remains for a long period of time after all symptoms of the anemia have responded satisfactorily to treatment

Loss of Body Weight—It is generally stated that patients with pernicious anemia are well nourished and this is often the case but it is by no means true in all instances. In fact usually patients state that they have

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Heart and Lungs —Examination of the lungs usually shows no abnormality unless there is an acute pneumonic process present which is sometimes seen when the anemia is advanced The heart is ordinarily normal or border line in size and when anemia is present there is almost always a soft systolic murmur heard at the apex or base or both areas For many years it has been recognized as hemic in nature As the anemia improves this disappears which is an indication that it is due to the alteration in the blood rather than a valvular lesion

Abdominal Examination—Liver and Spleen —The liver and spleen are usually not palpable although in the older descriptions of the disease apparently the latter organ was of sufficient size to be felt in a considerable number of patients In a review of our cases Bigg (*234*) stated that some authors reported the spleen to be palpable in 20 to 40 per cent of the cases In our group however he found this to be true in only 3 per cent of 200 patients with the disease In 18 of these patients in whom necropsies were performed the organ varied in weight from 95 to 640 grams with an average of 265 grams in 17 of the 18 patients it weighed more than the usually accepted normal weight of 150 grams *It is common therefore to observe some enlargement at necropsy but rarely is it increased to such a size as to be palpable during life* for it is known that it may be increased to four times normal and still not be felt on physical examination The presence of a palpable spleen therefore in patients suspected of having pernicious anemia should arouse suspicion that some other condition such as leukemia cirrhosis of the liver or some variety of hemolytic anemia may be present

The examination of the abdomen usually reveals nothing of importance except some evidence of weight loss but the exclusion of tumor masses which may be malignant in nature and thereby account for an anemia is important from the standpoint of differential diagnosis In some instances there is abdominal distension which may be striking in association with advanced spinal cord changes In other patients tenderness in the right upper quadrant may be evidence of an abnormal condition of the gall bladder

Edema —When the anemia is pronounced it is not uncommon to have slight to moderate pitting edema of the ankles present I have never observed ascites or hydrothorax which I felt sure was due to the anemia per se The cause of the edema is not always clear but it has been attributed to low plasma proteins to increased capillary permeability and to myocardial weakness

Fever and Secondary Thrombocytopenic Purpura —As the anemia becomes more severe two signs may appear unless prompt therapeutic measures are instituted They are fever and thrombocytopenic purpura With a red blood cell count below 2 5 million per cubic millimeter fever due to the anemia itself is commonly present but it usually does not exceed

lost from 20 to 25 pounds during the course of their illness They frequently appear well nourished despite the weight loss as they may previously have been overweight when the disease appeared The loss of weight is to be expected because so many of the patients have anorexia and commonly there is a slight amount of fever associated especially when the red blood cell count is low With the institution of adequate therapy the patient often develops a voracious appetite and the lost weight and often more is regained The disease however is not confined to persons who are obese as I have observed it but it does appear less commonly in those who are underweight

PHYSICAL EXAMINATION

General Description of Findings

Patients with this disease usually appear to be well nourished although as previously stated there is often a history of the loss of 20 to 25 pounds during the course of the illness There are exceptions to this but pronounced emaciation is not common

The degree of pallor of course depends upon the severity of the anemia It varies from the rather startling appearance of the pallor of death to a normal color of the skin when the red cell count is in the vicinity of normal There is almost always a delicate yellowish tint to the skin and conjunctivae when the red blood cell level is below 2 5 millions per cubic milimeter This may be difficult to detect even when it is known that the blood bilirubin is above the normal level A striking icterus is not observed in uncomplicated pernicious anemia and when present should suggest biliary obstruction or some variety of hemolytic jaundice

The hair of most patients with the disease is usually partially or wholly gray and the original color is most commonly light Likewise the eyes are frequently of the lighter shades of green gray or blue This is not always true for typical examples of the disease occur in dark complexioned persons

Tongue —Changes in the tongue are of great importance in the diagnosis of the disease As previously stated never in my experience have I seen a patient who had a definitely coated tongue when anemia was present This is striking when the red blood cell count is below a million per cubic millimeter and there is fever for then one would expect a heavy grayish brown coat to be present In some instances when complaints referable to the tongue are prevalent there may be a fiery red color involving the entire organ in other patients only the tip has a scarlet color In about one half of the patients the tongue has a smooth appearance due to atrophy of the papillae over the dorsum in some instances this may be localized in distribution

TABLE XVII

CEREBRAL MANIFESTATIONS IN 50 CASES OF PERNICIOUS ANEMIA (SPECIAL EXAMINATION)

	Incidence (Per Cent)
Irritability	64
Memory Disturbances	60
Mild Depression	58
Coma	18
Delusions	18
Hallucinations	16
Apathy	6
Maniacal Outbursts	2

TABLE XVII—The figures given above emphasize the frequency of various mental changes *which are more commonly present than is generally supposed* In part the changes may be due to (1) the prolonged effect of a severe anemia on the cerebrum (2) the psychic reaction to a chronic illness (3) various complicating factors such as cerebral arteriosclerosis (4) degenerative changes in the brain similar to those which occur in subacute combined degeneration of the spinal cord In general it may be said that many of the mental disturbances improve or disappear when the blood returns to normal but of course this is not always the case

tion and position ataxia is present and the same difficulty is experienced in walking as in tabes dorsalis A valuable differential sign from the latter condition however is the preservation of the deep pain sense as indicated by pinching the Achilles tendon in patients with pernicious anemia and its diminution or complete absence in tabes

Lateral column lesions manifest themselves by varying degrees of weakness spasticity and increased reflexes in the lower extremities a positive Babinski's sign and ankle clonus When the combined cord lesions are extensive the patient has a spastic ataxic paraplegia The degenerative changes in the spinal cord may progress to such an extent that they produce the lesions of a complete transverse myelitis

Loss of control of the sphincters usually confined to those of the urinary bladder is almost always a late sign in spinal cord involvement but is *taken as an indication of a degenerative change in the posterior columns* It should be considered as evidence of extensive pathologic change although control of the sphincters may be regained following treatment With a progression of the neurological involvement and loss of control of the bladder sphincters a resultant stasis of urine in the bladder with eventual infection of the urinary tract and a cystitis is likely to occur If such a condition is not checked there may be an ascending infection of the ureter and kidney with pyelitis abscesses of the kidney and in some instances a terminal septicemia

In a study (235) of a group of 408 of our patients it was found that neurological manifestations were present in approximately 90 per cent of the group Of these 43 per cent had the symptoms of nervous system

100 degrees (F) orally when the red count falls below one million per cubic millimeter it may rise to 101 to 104 (F) at which time it is likely to be associated with delirium. Other causes of fever however should be kept in mind, such as an infected urinary tract which is commonly seen in advanced spinal cord changes with urinary retention in the bladder and also with a complicating cholecystitis.

With a fall in the red blood cell count below 1.5 million per cubic millimeter evidence of bleeding in the skin mouth nose, and retinae may occur in association with a diminution of the blood platelets. As patients *with this disease are not now permitted to have an anemia of such a low* level persist for long intervals, due to the modern treatment such a hemorrhagic tendency is no longer commonly observed.

Neurological Manifestations.—A very large majority of patients with pernicious anemia have evidences of involvement of the nervous system which may be classified into the following four groups depending upon the extent of the changes. 1 Those with only paraesthesia of the four extremities which is probably due to peripheral neuritis 2 Those with paraesthesia and evidence of a lesion in the posterior columns of the spinal cord 3 Those with paraesthesia and symptoms and signs of posterior and lateral column involvement and 4 Those with changes enumerated in 3 plus loss of sphincter control of the urinary bladder or rectum or both.

Almost always the involvement of the different parts of the nervous system is the same order first the peripheral nerves then the posterior columns next the lateral columns and finally the loss of sphincter control. Exceptions of course have been noted to this order of involvement but they do not occur commonly.

Evidence of peripheral nerve changes is a persistent, progressive symmetrical numbness and tingling of all four extremities which is often exceedingly annoying to the patient but is not actual pain. In some patients there are likewise complaints of coldness and stiffness of the hands and feet. The numbness and tingling may vary in intensity from day to day but rarely disappears completely without treatment. This complaint which is so characteristic of patients with subacute combined degeneration of the cord is not commonly present in other conditions and hence is a valuable sign from a diagnostic standpoint. Never have I observed it to be present in only one extremity or the hands without the feet or vice versa. Always have all four extremities been involved. It has only been in recent years that the importance of peripheral nerve involvement has been recognized (*38 230 231*).

Lesions of the posterior column are indicated by the loss of the sense of motion and position and impairment or absence of the vibratory sense. This usually occurs in the lower extremities but in advanced cases these signs may extend to the arms. As a result of the loss of the sense of mo

TABLE XVII

CEREBRAL MANIFESTATIONS IN [illegible]0 CASES OF PERNICIOUS ANEMIA (SPECIAL EXAMINATION)

	Incidence (Per Cent)
Irritability	64
Memory Disturbances	60
Mild Depression	58
Coma	19
Delusions	18
Hallucinations	16
Apathy	6
Maniacal Outbursts	2

TABLE XVII.—The figures given above emphasize the frequency of various mental changes which are more commonly present than is generally supposed. In part the changes may be due to (1) the prolonged effect of a severe anemia on the cerebrum, (2) the psychic reaction to a chronic illness, (3) various complicating factors such as cerebral arteriosclerosis, (4) degenerative changes in the brain similar to those which occur in subacute combined degeneration of the spinal cord. In general it may be said that many of the mental disturbances improve or disappear when the blood returns to normal but of course this is not always the case.

tion and position, ataxia is present and the same difficulty is experienced in walking as in tabes dorsalis. A valuable differential sign from the latter condition, however, is the preservation of the deep pain sense as indicated by pinching the Achilles tendon in patients with pernicious anemia and its diminution or complete absence in tabes.

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In a study (235) of a group of 408 of our patients it was found that neurological manifestations were present in approximately 90 per cent of the group. Of these 43 per cent had the symptoms of nervous system

involvement at the onset of the disease, and in 46 per cent they developed during the course of the illness but before the patient came under our observation In an appreciable per cent of patients they were the initial *evidence of the disorder, and the first symptom to direct the patient's* attention to the disease Evidences of combined degeneration was present in 40 7 per cent

The most common neurological manifestations in our group were as follows numbness of the extremities 90 per cent, tingling of hands and feet 80 per cent loss of finer coordination of the fingers 64 per cent ataxia 64 per cent Rombergism 62 per cent and Babinski reflex 56 per cent The more frequently observed cerebral complaints were irritability 64 per cent memory disturbance 60 per cent and mild depression 58 per cent (See Table XVII) Other important but less frequently en*countered evidences of neurological involvements were loss of position* sense 42 per cent decrease or loss of vibratory sense 48 per cent stiffness of lower extremities 42 per cent and increased knee jerks 38 per cent Other less common symptoms and signs were ankle jerks increased 28 per cent band sensations 26 per cent, astereognosis 26 per cent ankle jerks decreased or absent 24 per cent decreased knee jerks 18 per cent bladder disturbance 8 per cent cutaneous hyperaesthesia and anaesthesia to touch pain and temperature approximately 8 per cent

It is not common to observe involvement of the special senses although tinnitus and visual disturbances may occur as a result of the anemia Optic atrophy *is a rare complication (236)*

With the more efficient treatment of pernicious anemia especially since the introduction of refined liver extract for intramuscular use the disease has been much better controlled Hence advanced neurologic changes are less commonly observed This gratifying evidence of more efficient treatment of pernicious anemia is likely to become even more apparent in the immediate future

LABORATORY EXAMINATIONS

Changes in the Blood

The Hemoglobin, Red Blood Cell Count, and Color Index —The red blood cell count varies from below one million per cubic millimeter to normal depending upon the stage of the disease and the nature of the patient's complaints when consulting a physician Symptoms arising from the anemia are slight when the count is as high as 3 5 million per cubic millimeter somewhat more pronounced when it is 3 million and definite when it is less than 2 million Below one million the patient's *strength is so reduced that only limited activities* are possible and almost complete bed rest is imperative The lowest count that I have observed in a patient was 480 000 per cubic millimeter which was subsequently restored to normal by liver therapy

The hemoglobin content of the erythrocytes is almost always relatively high and as a result the color index is usually 1 0 or greater With a red blood cell count of 3 5 million per cubic millimeter the hemoglobin is likely to be between 70 and 80 per cent 10 9 to 12 5 grams with a count of 2 million between 40 and 50 per cent 6 3 to 7 8 grams and with 1 million between 20 and 30 per cent 3 1 to 4 7 grams The color index even when the hemoglobin is uncorrected for age and sex is usually 1 0 or higher in patients with pernicious anemia if it is significantly below 1 0 then the patient either does not have the disease or some complication is present such as hemorrhage or an associated deficiency in the intake of iron When effective therapy is administered however the regeneration of red blood cells is more rapid than the formation of hemoglobin and

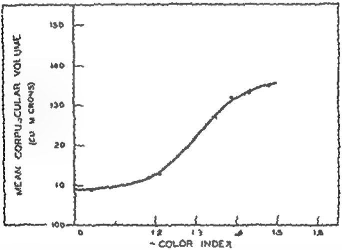

Fig 29 —Chart showing the relationship between the color index and the mean corpuscular volume in patients with pernicious anemia The curve shows that in general the greater the M C V the higher the color index but some exceptions will be noted to this statement in the above chart

consequently the color index usually falls as the erythrocyte count approaches normal Subsequently the lag in hemoglobin formation is overcome and the color index again becomes 1 0 Only occasionally it is necessary to add iron to the liver therapy in order to restore the hemoglobin level to normal

Changes in Size and Shape Macrocytosis —The most characteristic finding in the blood of patients with this disease is the presence of a variable number of large oval erythrocytes which stain somewhat darker than the average red blood cell These are called macrocytes and a macrocytosis is the most constant finding in the blood of patients with pernicious anemia When the red blood cell count is below normal these

cells usually make up from 10 to 30 per cent of all red blood cells and their number is roughly proportional to the severity of the anemia. The macrocytosis of pernicious anemia is the earliest change which takes place when the level of the red cells falls and it is the last one to disappear as the count rises from the anemia stage to normal. It is an alteration in the blood which is readily apparent to the trained hematologist but it is often overlooked by the less experienced and hence a blood film which has a definite macrocytosis may be reported as normal. Macrocytes vary from 8.5 microns to as large as 15 microns in their greatest diameter.

In addition to macrocytes there are almost always small cells present in variable numbers which are called microcytes. These measure from 3 to 5 microns. Anisocytosis in a blood film usually in the same oil immersion field due to the presence of macrocytes and microcytes is characteristic of pernicious anemia and is always present when the anemia is pronounced.

Likewise striking and often bizzarre changes in shape or poikilocytosis are invariably present in the blood when a definite anemia is present. Both anisocytosis and poikilocytosis are most pronounced when the red blood cell count is 1.5 million per cubic millimeter or less.

Volume Measurements of the Red Blood Cells and Their Hemoglobin Content.—The changes in the size of the red blood cells and their hemoglobin content are best expressed quantitatively by calculations involving the red blood cell count, the hematocrit determination and the hemoglobin estimation in grams per 100 cc of blood. The average volume for example is determined by dividing the volume of packed red cells (cc per 1000) by the red blood cell count in millions per cubic millimeter. This gives the mean corpuscular volume (M.C.V.) which normally varies between 86 and 96 cubic microns. In pernicious anemia it is increased and in general it may be said that the more severe the anemia the greater the mean compuscular volume. Reading of between 110 and 140 cubic microns are usually observed when the anemia is moderately severe. There is however one exception to this statement namely that when the red blood cell count falls below a million per cubic millimeter the mean corpuscular volume is often not greatly increased as at this level there are many microcytes present which of course reduces the average volume of the cells. Often under these circumstances the mean corpuscular volume is between 110 and 115 cubic microns.

The relationship of the hemoglobin content of the cells to the volume is also a useful method of expressing the changes which occur in pernicious anemia and other anemias. This is best expressed by means of the mean corpuscular hemoglobin concentration (M.C.H.C.). It is determined by dividing the hemoglobin in grams per 100 cc multiplied by 100 by the volume of packed cells cc per 100 cc. Normally this value is between 30 and 32 micromilligrams in pernicious anemia it is

between 30 and 35 micromilligrams In hypochromic anemias it is below 30 and may be as low as 26 micromilligrams

The Price Jones method of measurements of the red blood cells is an excellent procedure for indicating the presence of both microcytes and macrocytes in the blood and their percentages but it is more laborious than determining the erythrocyte count and volume determinations by means of the hematocrit These measurements are made by determining the diameters of 200 red blood cells and charting them according to the percentage of cells with certain diameters When so plotted there are three changes from normal which are characteristic of the blood of patients with pernicious anemia with a low red blood cell count They are (1) That the two legs of the curve are widely separated this is because there are both very small and very large red blood cells present (2) The curve is not smooth as in the case of the measurements of normal erythrocytes but it is jagged and (3) The peak of the curve is about 9 5 microns as contrasted to the peak in normal blood which is usually about 7 5 microns

Immature Forms of Red Blood Cells—All forms of immature red blood cells may appear on the peripheral blood of patients with pernicious anemia *but they never occur unless the blood is in the regenerative phase* This is seen when the patients are either in a spontaneous or therapeutically induced remission and hence is not so helpful from the standpoint of diagnosis as the patients are not likely to consult a physician when they are improving There is one exception to this statement however and that is at Simpson Memorial Institute we not infrequently see patients with pernicious anemia who have recently consulted their local physician who suspects but is not sure that the patient is suffering from pernicious anemia and hence refers him for consultation In his desire to initiate helpful therapeutic measures at once one injection of liver extract may be given intramuscularly several days before the patient is observed by us and at this time the liver extract will have had its effect Consequently under these circumstances it is not unusual to observe immature erythrocytes of all types in the blood Among these cells are normoblasts and occasionally megaloblasts cells with punctate and diffuse basophilia and those with Cabot s ring forms and Howell Jolly bodies The most constant change however is an increase in the percentage of reticulocytes which is apparent when the film is stained with a vital stain such as cresyl blue

The Leukocytes—In pernicious anemia during a relapse there is characteristically a leukopenia which usually varies from 3500 to 6000 white blood cells per cubic millimeter This reduction in the total white blood cell count is due largely to a diminution in the number of neutrophils often to 40 or 50 per cent so that it may properly be spoken of as a neutropenia Another characteristic finding is that the nuclei of a large

proportion of the neutrophils have from four to six or more lobes indicating that they are older than those which are normally encountered in blood

It is interesting to note that if a patient with untreated pernicious anemia develops an infection which ordinarily evokes a leukocytosis *there is usually no increase in the number of white blood cells* If such an infection is present and the patient is given antipernicious anemia therapy however then there is an immediate and often very extensive *rise in the number of polymorphonuclear leukocytes* In one patient whom I saw with a severe infection there was an increase in the leukocytes from a count below normal to 50 000 per cubic millimeter chiefly *neutrophils within 30 hours after an injection of liver extract* The only other circumstance in which there probably would be a response of the neutrophils to an infection in a patient with pernicious anemia would be the *fortuitous development of a spontaneous remission* Occasionally elevated white blood cell counts have been reported in patients with pernicious anemia in relapse without an infection and unrelated to therapy Such a circumstance would arouse considerable suspicion in my mind that either the diagnosis of pernicious anemia was incorrect or that nucleated red cells had been improperly enumerated as leukocytes in the counting chamber

Blood Platelets —A decrease in the circulating blood platelets is constantly observed during relapse and this parallels in a general way the severity of the anemia When the red blood cell count is extremely low there is a corresponding diminution in the platelets and in some instances a secondary thrombocytopenic purpura develops After therapy the increase in platelets follows that of the erythrocytes Paddock and Smith (237) have reviewed the subject of the platelets in this disease and conclude that the thrombopenia associated with pernicious anemia in relapse is not a differentiating feature from other macrocytic anemias

Hyperbilirubinemia —It is now well recognized that patients with the disease in relapse have an increase in the bilirubin of the blood plasma and that there is a rough inverse relationship correlation between the level of the blood bilirubin and the severity of the anemia The increased bilirubin accounts for the yellowish pallor or lemon yellow color of these patients

The two *clinical methods which are employed in estimating the bilirubin* are the quantitative van den Bergh reaction and the icterus index The highest level of normal with the former is 0 7 mg per 100 cc of *blood and with the latter four to six units* In pernicious anemia in relapse the van den Bergh method gives readings between 1 and 3 mg and the icterus index from 20 to 25 units These increased values become normal during remissions (Further discussion of the metabolism of the bile pigments will be found in the section dealing with the role of hemolysis in the production of the anemia of pernicious anemia on page 271

In the past it has been held by some that a rise in the circulating bilirubin is an indication of increased blood destruction. This is not necessarily true however for it may be due to impaired hepatic cell function possibly resulting from anoxemia

Prothrombin Level of the Blood—According to Warner and Owen (238) the prothrombin level in the blood of patients with this disease is below normal when an anemia is present although the decrease is not marked They found when the two stage method of Warner Brinkhaus and Smith was employed that the level was between 40 and 65 per cent of normal in most patients Vitamin K either orally or intravenously did not change the levels which leads them to suggest that the deficiency of prothrombin may be attributed to hepatic damage There is a tendency for the lowest prothrombin levels to be present in patients with the most severe anemia The deficiency of prothrombin may explain in some instances the tendency of patients with pernicious anemia to bleed abnormally although this is usually attributed to a decreased number of platelets

Achlorhydria—An achlorhydria is the most constant finding in the disease and the diagnosis of pernicious anemia in my opinion should be eliminated from consideration if free hydrochloric acid is found in the gastric secretions provided one is certain about the technical aspects of the test It is also true that with the achlorhydria there is likewise constant lack of pepsin in the gastric secretions Not only can I state that in my experience there has *always been an achlorhydria in all patients with pernicious anemia but never does free hydrochloric acid return during either therapeutically induced or spontaneous remissions Furthermore in all instances in which a gastric analysis has been done prior to the development of the disease there has likewise been a persistent achlorhydria* One of my patients a physician who previously had a gastric analysis done 25 years before evidence of pernicious anemia developed was found to have an achlorhydria at that time Certainly sufficient evidence is at hand to state positively that patients with pernicious anemia do not have free hydrochloric acid present in the gastric secretion when they have evidence of the disease Also it is probably true that they have a persistent achlorhydria since birth and that acid does not return in the gastric juice when they are treated The latter two claims however require further confirmation but I can say that in my own experience there have been no exceptions to this statement

It must be admitted that a small group of cases have been reported as having free hydrochloric acid in the stomach secretions and in these one cannot help but think that possibly some other cause for the macrocytic anemia had been overlooked In some instances this might have been cirrhosis of the liver which is capable of producing a blood picture closely simulating pernicious anemia and one which likewise responds to the

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factor must be shown to be *idiopathic* by the exclusion of the other conditions which may induce it. It is recognized by Askey that it is impracticable to demonstrate reduction in the specific liver principle. Direct studies by biologic assay of the liver can be made only in the fatal cases. Indirect data obtained by the response of the patient to the administration of liver extract is not entirely acceptable according to this investigator. In his opinion the liver extract usually used is Cohn's fraction G which contains not only the specific antipernicious anemia principle but also different fractions which have been shown to be effective in nutritional macrocytic anemia of the tropics. According to him it is impossible to know, therefore, whether improvement of a macrocytic anemia following the administration of Cohn's fraction G is due to the specific antipernicious anemia fraction or the fraction effective against nutritional macrocytic anemia. He suggests that if the response to liver is used as a therapeutic test, a favorable effect is of little significance unless the Dakin West fraction or one of the other highly purified fractions obtained from the original Cohn's fraction G is used. He assumes that response to desiccated hog stomach or ventriculin would be a more precise therapeutic test.

In a consideration of 47 reports in the literature of cases of pernicious anemia without achlorhydria he has concluded that 32 of these cases are unacceptable because other causes for the anemia were present, or the data were unconvincing. It is his final opinion that it has *never been established beyond doubt* that addisonian pernicious anemia can exist with persistence of secretion of hydrochloric acid. The diagnosis of addisonian pernicious anemia, therefore, without achlorhydria has been a presumption, not an established fact. It is his opinion that the existence of true pernicious anemia without anacidity as yet cannot be accepted. In this belief I am in complete accord. Certainly the presence of hydrochloric acid in the gastric secretions of patients suspected of having pernicious anemia raises objection to the diagnosis, and some other explanation of the associated macrocytic anemia should be sought.

A most careful and extended study of one case of a patient with macrocytic anemia in which free hydrochloric acid was present in the gastric secretions, along with an extensive review of the literature bearing on the subject, is reported by Murphy (242). It was considered by this observer that this patient, who was followed over a period of nine years, did have true addisonian pernicious anemia. Furthermore, tests were performed which indicated that the intrinsic factor was absent from the gastric secretions. There are some features which Murphy recognizes that are against, but do not eliminate, the diagnosis of pernicious anemia. For example, the patient was only 23 years of age, no neurological changes were present, and glossitis was absent. Furthermore, the author appreciates that he did not demonstrate the characteristic megaloblastic change

intramuscular injections of liver extract In other cases possibly the anemia may have been accounted for by some intestinal abnormality such as an anastomosis or stricture In our own group of patients one was regarded as having pernicious anemia until necropsy showed evidences of cirrhosis of the liver and another patient had a macrocytic anemia which responded rather atypically to liver therapy, but subsequently the condition was found to be a subleukemic leukemia in which the diagnosis became obvious when one year later the white blood cell count became greatly elevated

Samuel A Levine co author with W S Ladd of one of the most complete and early papers (*239*) on the relation of achlorhydria to the disease, told me (*240*) that in only one of the 107 patients with pernicious anemia whom he examined had free acid been present and in this patient there is some question in his mind as to whether the correct specimen of gastric secretion was examined According to him there are 16 similar specimens of gastric contents sent to the same laboratory on the day of the test in question and the possibility must be considered that there was some error in the labeling of the specimen glasses When free acid was noted in the sample from the patient with pernicious anemia he made an attempt to secure another sample but this was impossible on account of the patient s serious condition At necropsy there did not seem to be any doubt concerning the diagnosis of pernicious anemia but no free acid was then found in the gastric secretions The details concerning this case have been given because reference has been made to it in the literature as evidence that a patient with proven pernicious anemia can have free acid in the gastric secretions Again it should be stated emphatically that the presence of free hydrochloric acid casts serious doubt on the diagnosis of pernicious anemia and should lead one to consider strongly some other cause for the macrocytic anemia

When one reports a case of pernicious anemia in which it is claimed that hydrochloric acid is present in the gastric juice it becomes necessary in the opinion of Askey (*241*) first to exclude all the other causes of macrocytic anemia second to demonstrate the absence of the intrinsic factor and finally to prove that the anemia is due to a deficiency of the specific antipernicious anemia liver factor The presence of cirrhosis of the liver extreme hypothyroidism pregnancy sprue pellagra gastric neoplasm intestinal strictures and anastomoses or gross nutritional deficiencies are all adequate causes for macrocytic anemia These must be excluded before the diagnosis of true pernicious anemia is acceptable According to Askey (*241*) a reduction in the gastric intrinsic factor may be associated with pregnancy gastric neoplasm sprue intestinal strictures ulcers and avitaminosis and the mechanism of the production of the macrocytic anemia in these conditions is not the same as in addisonian pernicious anemia To be significant therefore the loss of the intrinsic

one should carefully inspect the stools for the presence of ova and segments of *Diphyllobothrium* latum. Also the characteristic stools of idiopathic steatorrhea and sprue should be kept in mind and a macrocytic anemia from these causes be excluded.

It is also essential that the stools be studied for occult blood which might indicate the presence of malignancy of the gastrointestinal tract as this occasionally may produce a blood picture similar to pernicious anemia.

In a study of stools Nye (245) found that there was a great increase in the number of *B. welchii* spores as compared with normal stools and those from a majority of patients with miscellaneous diseases. It is of importance to note, however, that Nye found the same increase in these spores also present in stools from cases of achylia gastrica without pernicious anemia. On the basis of these observations and the tendency of *B. welchii* to form spores in alkaline media, it seems logical to assume that the spore increase in pernicious anemia is secondary to the gastric achylia rather than indicative that pernicious anemia is caused by chronic intestinal infection with *B. welchii*. Although the growth of *B. welchii* was thought to be related to the etiology of pernicious anemia, this view is no longer held by those who have studied the question carefully.

DIFFERENTIAL DIAGNOSIS

According to Askey (246), the diagnosis of pernicious anemia is not acceptable unless there is present a primary composite triad of essential criteria consisting of (1) a persistent histamine refractory anacidity, (2) a permanent decrease of Castle's intrinsic factor, and (3) a reduction of the stored antipernicious anemia principle. While his arguments favoring the rigidity of the criteria in evaluating patients with macrocytic anemia are undoubtedly sound, nevertheless it is not practical to apply them routinely. Askey considers that the natural history of pernicious anemia is indicated by the orderly development of anacidity followed by the loss of intrinsic factor and finally the loss of antipernicious anemia principle. While this may be correct, it certainly is an assumption. It is easy to determine the presence or absence of a histamine refractory anacidity and this of course should be done in all patients suspected of having the disease. When it comes to determining a reduction in Castle's intrinsic factor and a reduction in the antipernicious anemia principle, many difficulties are encountered. It is possible and in a few cases it has been demonstrated that the intrinsic factor is diminished (247), but this requires a special technic which of course cannot be applied routinely in practice. Likewise it is not possible with ease to demonstrate precisely that there is a diminution of the antipernicious principle. It is assumed by many that a response to liver extract is proof of this but as Askey (246) points out, the macrocytic anemia of

in the bone marrow Nevertheless he has observed and studied in careful detail a patient in whom the association of addisonian pernicious anemia and free hydrochloric acid in the gastric secretion was more likely than in any case previously reported

Not only do patients with pernicious anemia have an absence of hydrochloric acid but also the total amount of the secretion is small the pH of the secretion is high and there is also a total absence of pepsin According to Goldhamer (243) patients with the disease have a volume secretion averaging about 20 cc per hour whereas the average normal secretion is 150 cc per hour He believes that the volume of the gastric secretion in relapse is dependent primarily on the severity of the disease process and less on the age of the subjects whereas in remissions the gastric juice volume appears to be related to age

It should be emphasized that gastric analysis in patients with pernicious anemia should always be done following the administration of 0 5 mg of histamine which is a powerful stimulus to gastric secretion In some instances in my experience patients have been referred for an opinion concerning the diagnosis of pernicious anemia with a statement that an achlorhydria has been present following a test meal It has sometimes been possible in such patients to demonstrate free acid in the gastric juice following the injection of histamine Such evidence as previously emphasized practically eliminates the diagnosis of pernicious anemia from consideration

Urine and Kidney Function Tests —Over one half of the patients with pernicious anemia have a slight to moderate albuminuria and a few hyaline and granular casts in the urinary sediment This may be in part because these findings are not uncommon in persons of the age when the disease commonly develops When the anemia is severe the specific gravity of the urine is low and fixed This disappears when the blood returns to normal in most instances Rarely is the blood non protein nitrogen elevated above normal limits and the phenolsulfone phthalein excretion is not impaired although the urea clearance is low during relapse but usually returns to normal in remissions

The color of the urine is usually pale but it may be dark orange when excessive amounts of urobilin are excreted

Stools —There are no characteristic changes in the stools in patients with pernicious anemia In many cases they are entirely normal in every respect provided diarrhea is absent When this is present the feces are often of a light tan color which has been attributed to an excess of stercobilin (244) In patients with severe diarrhea there may be an excess of mucus and some pus and occasionally occult blood may be present

The chief value in the examination of the stools is to eliminate other conditions which might be responsible for a macrocytic anemia Hence

In the days prior to effective treatment that is before 1926 a history of spontaneous remissions was of assistance in making the diagnosis One or more of these almost always occurred in the course of the disease without reference to treatment or any other known variation in diet habits or environment As the disease is now rarely permitted to pursue its natural spontaneous course because effective therapy is instituted as soon as the condition is recognized there is little chance to observe remissions other than those which are induced by treatment A history of a sudden and often dramatic improvement following anti pernicious anemia therapy is of course often of help in arriving at the proper diagnosis of pernicious anemia in any given case

There are in the blood of patients with pernicious anemia certain characteristic changes which are almost invariably present in all cases and they serve therefore as invaluable aids in the diagnosis These are the macrocytosis the increase in the mean corpuscular volume which is always above 100 cubic microns and often between 110 and 130 cubic microns and may be higher the leukopenia with a decrease in the neutrophils the characteristic neutrophils with their multilobed nuclei the poikilocytosis and anisocytosis and the striking increase in the reticulocytes following the administration of liver extract or other potent anti-pernicious anemia therapy All of these when considered together with the various features of the history and physical examination make it possible to recognize the disorder with a high degree of accuracy The correct diagnosis is not always achieved however as indicated by the information obtained by Hardgrove and his associates They found that in over one half of their patients the disease was not recognized by the first physician they consulted although suggestive symptoms were present Moreover in 11 25 per cent of their patients the first three physicians consulted were unable to make a diagnosis It is of significance as an explanation of these deficiencies in the diagnosis that 86 25 per cent in their group were not adequately studied until they were hospitalized

A group of young adults with atypical pernicious anemia has been reported by Schwartz and Legere (248) which bring up some interesting points from a diagnostic standpoint A macrocytic anemia achlorhydria and a specific response to liver therapy occurred in all patients The manifestations of the condition were sufficiently atypical however as to cause diagnostic difficulties Among the more significant variations was the occurrence in the younger age group (seven of the nine were between 25 and 31 years of age) the frequency in Negroes (five of the nine patients) the apparent acuteness of the onset the misleading prominence of the cardiac symptoms the febrile course so suggestive of infection and the conspicuous paucity of neurological complaints It should be emphasized also that there was no history of re

India responds to crude liver extract but not to the purified Dakin West fraction He concludes that the Cohn fraction G contains two distinct anti macrocytic anemia principles namely (1) the specific pernicious anemia principle and (2) the anti macrocytic principle effective in tropical macrocytic anemia In the fatal cases a deficiency of this principle has been demonstrated by the preparation and testing of a liver extract obtained at necropsy In my opinion the observations upon which these statements are based, and their interpretation must be accepted with caution

The *diagnosis of pernicious anemia* in most instances can be made with a certainty provided a sufficient period of time is given to observe the patient, and especially if it is possible to try the effect of antipernicious anemia therapy *In general it may be said that if a person of middle age or older has recently developed a pronounced pallor with a definite*

TABLE XVIII

FREQUENCY OF CERTAIN DIAGNOSTIC FEATURES IN PERNICIOUS ANEMIA

	Per Cent
1 Achlorhydria	100
2 Macrocytosis	90+
3 Response to Treatm nt	100
4 High Color Index	80+
5 Paraesthesia	90
6 Glossitis	65
7 Absence of Leucocytosis	90

TABLE XVIII —The above table shows the seven most common diagnostic features in patients with pernicious anemia By achlorhydria is meant the absence of free HCl in the gastric secretions following the subcutaneous injection of 0 5 milligram of histamine phosphate A macrocytosis indicates a mean corpuscular volume which exceeds 96 cubic microns and in some instances is as great as 140 cubic microns the average of the group observed was be tween 115 and 120 cubic microns Response to treatment was judged by an adequate rise in the reticulocytes red blood cells and hemoglobin of the circulating blood associated with a sense of well being and a disappearance of the major symptoms of the disease A high color index is one which varies from 1 0 to 1 5 By a glossitis is meant attacks of sore tongue which are recurrent not attributable to any other cause and cured by antipernicious anemia therapy The absence of leukocytosis implies a white blood cell count which is always below 10 000 and frequently less than 6000 per cubic millimeter Even in the presence of infection there is no increase in the white blood cell count unless the patient has an associated spon taneous or therapeutically induced remission

yellowish tint there is a possibility that the condition is one of per nicious anemia If in addition there is an achlorhydria as determined after the injection of histamine and paraesthesia of the hands and feet one can say that it is likely that the patient has pernicious anemia even before the blood is examined

Other evidences of the disease which are important from a diagnostic standpoint, are the attacks of *recurring glossitis* about which approxi mately two thirds of the patients complain and a *smooth atrophic tongue* which is present in approximately one half of the cases

In the days prior to effective treatment that is before 1926 a history of spontaneous remissions was of assistance in making the diagnosis. One or more of these almost always occurred in the course of the disease without reference to treatment or any other known variation in diet habits or environment. As the disease is now rarely permitted to pursue its natural spontaneous course because effective therapy is instituted as soon as the condition is recognized there is little chance to observe remissions other than those which are induced by treatment. A history of a sudden and often dramatic improvement following antipernicious anemia therapy is of course often of help in arriving at the proper diagnosis of pernicious anemia in any given case.

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A group of young adults with atypical pernicious anemia has been reported by Schwartz and Legere (248) which bring up some interesting points from a diagnostic standpoint. A macrocytic anemia achlorhydria and a specific response to liver therapy occurred in all patients. The manifestations of the condition were sufficiently atypical however as to cause diagnostic difficulties. Among the more significant variations was the occurrence in the younger age group (seven of the nine were between 25 and 31 years of age) the frequency in Negroes (five of the nine patients) the apparent acuteness of the onset the misleading prominence of the cardiac symptoms the febrile course so suggestive of infection and the conspicuous paucity of neurological complaints. It should be emphasized also that there was no history of re

current glossitis and that the spleen was palpable in seven of the nine patients Nevertheless these patients had some of the important and constant symptoms of pernicious anemia including a satisfactory response to antipernicious anemia therapy hence the importance of considering the diagnosis of the disease in the presence of any severe anemia

There are, however certain other macrocytic anemias which should always be kept in mind when the diagnosis of pernicious anemia is under consideration They are the anemias associated with the following conditions *Diphyllobothrium* latum infestation various short circuiting operations and stricture of the intestines cirrhosis of the liver extensive neoplastic infiltration of the stomach as in linitis plastica sprue some cases of pellagra myxedema subleukemic leukemia various nutritional anemias and the macrocytic anemia observed in association with pregnancy

When considering the diagnosis of the above types of macrocytic anemia it is well to remember the following facts concerning the disease it does not occur commonly in persons under 40 years of age *never* does pernicious anemia exist *in the absence of an achlorhydria* *rarely* is it present in the absence of both paresthesia of the hands and feet and recurrent glossitis the presence of an easily palpable spleen is very much against the diagnosis a leukopenia and poikilocytosis are invariably present if the red blood cell count is 2 5 million per cubic millimeter or less and it almost always responds with a characteristic reticulocyte rise following the proper therapy

Most patients with pernicious anemia should have a complete gastrointestinal x ray series done including cholecystography This is because in rare instances the stomach may be so infiltrated with a neoplasm that a decrease in the secretion of the intrinsic factor occurs which results in the picture of pernicious anemia in the circulating blood Another reason is because stricture of the intestines and short circuiting operations may also produce a blood picture which is indistinguishable from pernicious anemia And finally abnormalities of the gallbladder such as can be demonstrated by a cholecystogram are often present in patients with pernicious anemia Furthermore the presence of gall stones in a patient with an anemia should direct some attention to the diagnosis of a hemolytic anemia especially to the hereditary variety in which they occur commonly

Subleukemic Leukemia —This condition is not infrequently confused with pernicious anemia and it is not rare to have a patient with this malady referred to the Simpson Institute with a statement that the patient *has pernicious anemia which does not respond properly* to the usual effective therapy In some instances pernicious anemia can be ruled out immediately because free hydrochloric acid is found in the gastric secretions In other patients a generalized lymph glandular enlargement

or an enlarged spleen is detectable which suggests the diagnosis of leukemia rather than pernicious anemia. The confusion in diagnosis arises because it is possible for a patient to have subleukemic leukemia with an achlorhydria with a macrocytic anemia and an absence of splenic or lymph gland enlargement. Never have I seen a patient with subleukemic leukemia who has had a symmetrical and persistent paraesthesia of the hands and feet or with a sore tongue; furthermore the mean corpuscular volume is not greatly increased in this disease as it is in pernicious anemia but is usually in the vicinity of 100 cubic microns; and finally in this condition there is not the typical reticulocyte response which is uniformly evoked in patients with pernicious anemia by liver

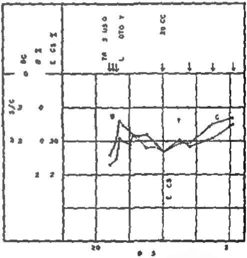

Fig 30.—This patient W T M No 233392 a male age 40 had cirrhosis of the liver which was proven by abdominal operation and biopsy of the liver. Before antipernicious anemia therapy was begun the red blood cell count was 1.66 millions per cubic millimeter and the hemoglobin 26 per cent. Two blood transfusions were given and later intravenous liver extract was administered as indicated on the chart. As a result of the liver therapy the reticulocytes increased to 36 per cent at which time the patient left the hospital. Subsequently with additional intravenous treatments of liver extract the patient's blood returned to normal. The blood was not maintained at the normal level because the patient became lax in following directions. (Sturgis and Goldhamer courtesy *Annals of Internal Medicine*.)

or stomach therapy. Moreover a sternal puncture or biopsy will usually clinch the diagnosis of subleukemic leukemia as in this condition there is commonly an infiltration with leukemic cells in the marrow whereas in pernicious anemia the findings are those of a maturation arrest of the erythrocyte series at the megalocyte stage.

Diphyllobothrium Latum.—This infestation is capable of producing a blood picture which is identical with the addisonian pernicious anemia but it may be differentiated because the ova and segments of the tape worm are easily identified in the stools. It is not common in North America but cases have been observed in persons who have acquired the condition in their native land and have carried it for some years. Also it is now recognized that infestation has been acquired from fish eaten in the United States. The late A. S. Warthin proved that at least a

few fish of Lake St Claire, Michigan harbored this parasite

Cirrhosis of the Liver.—With extensive liver damage as occurs in cirrhosis of the liver, and when uncomplicated by excessive hemorrhage from esophageal varices, there may be an associated macrocytic anemia but rarely with a megaloblastic bone marrow, which resembles pernicious anemia In some instances there may also be a glossitis apparently due to a vitamin deficiency which is often seen in these patients When this occurs in a patient with cirrhosis who has an achlorhydria and does not have ascites, the clinical picture may be confusing Liver function tests however, make the diagnosis at once apparent

Sprue.—In this condition which may resemble pernicious anemia closely, there is a megaloblastic bone marrow and in 90 per cent of the cases a macrocytic anemia which is responsive to liver therapy. It is not observed however in the northern part of the United States although the so called non tropical sprue is sometimes encountered in this region Furthermore, free acid may be present in the gastric juice of patients with this disease and neurological manifestations of pernicious anemia are rarely present Moreover one of the outstanding clinical features *of sprue is the disturbances referable to the gastro intestinal tract* namely dyspepsia and the passage of liquid foamy grayish foul smelling frequently voluminous and fatty stools

Pellagra and Other Macrocytic Anemias Due to a Deficiency of the Extrinsic Factor.—Every patient with pernicious anemia should have a careful dietary history taken because some cases of pellagra may closely simulate the condition Outspoken pellagra may be recognized by the characteristic symmetrical skin lesions especially of the hands the elbows and over the knees Furthermore in some cases apparently the macrocytic blood picture results from a decrease in the extrinsic factor in the dietary intake This is also one explanation of the macrocytic anemia in sprue as the stomach in this condition is not at fault The fact that approximately 25 per cent of patients with pernicious anemia respond when given yeast in fairly large doses also suggests that at least in these patients the macrocytic anemia arises in part from a deficiency of the extrinsic rather than of the intrinsic factor In the pernicious anemia of pregnancy evidence is now available which suggests that it may result from a deficiency of protein in the diet (249) it is possible also that the condition may be associated with an inadequate folic acid intake This condition has a blood picture which closely simulates that of pernicious anemia but varies from it in that neurological changes are not present free acid may be found in the gastric juice the anemia disappears entirely following pregnancy and may not reappear in some cases in subsequent pregnancies

Myxedema.—A macrocytic anemia commonly occurs in patients with myxedema but usually the mean corpuscular volume is not increased to

more than 110 cubic millimeters In rare instances however it has been definitely proven that the two diseases co exist In most patients I have observed in whom the diagnosis has been confused they have been treated for pernicious anemia when they have been suffering from myxedema despite that fact that the diagnosis has been fairly obvious from the general appearance of the patient About one half of the patients with myxedema have an achlorhydria which adds to confusion in the diagnosis In no instance however have I observed a glossitis or neurological changes characteristic of pernicious anemia Furthermore the macrocytic anemia of myxedema is usually only of a moderate extent and does not respond to antipernicious anemia therapy And finally the diagnosis of myxedema can be clinched by determining that a low basal metabolic rate is present and a blood cholesterol which is usually greater than 300 milligrams per 100 cc of plasma In pernicious anemia both of these determinations are usually within normal limits although the basal metabolic rate in pernicious anemia may be slightly elevated when the anemia is severe

Nephritis—In some instances patients suffering with chronic glomerular nephritis and the commonly associated anemia have been regarded as having pernicious anemia Superficially patients with this condition may resemble those with pernicious anemia but usually even after a cursory examination it is easy to differentiate the two diseases Furthermore in chronic nephritis the anemia is normocytic rather than macrocytic Although the urine of patients with pernicious anemia may have a low and fixed specific gravity and a decrease in the urea clearance usually the phenolsulfonephthalein test is within normal limits and there is no increase in the non protein nitrogen of the blood or the blood urea nitrogen The changes in the fundi as detected by the ophthalmoscope should differentiate the two conditions And finally the anemia of nephritis shows no response to antipernicious anemia therapy

Other Diseases Associated with Pernicious Anemia—As pernicious anemia is likely to be present at middle life or later when certain other diseases are prevalent it is to be expected that there should be associated with it certain maladies common to that age group In my experience these may be divided into the following three groups

I Those diseases which are related etiologically with pernicious anemia as follows gallbladder disorders cystitis and sometimes pyelitis mild mental disturbances and changes in the spinal cord

II Those which have only a fortuitous association with pernicious anemia The more important of these are hypertension and arteriosclerosis cardiac disorders malignancy arthritis and vitiligo There are of course many other conditions which occur commonly during the years of the greatest incidence of pernicious anemia any of which may develop simultaneously with pernicious anemia in the same patient

III Certain diseases about which there has been some discussion as to whether they occur in some instances with greater and in others with less incidence in patients with pernicious anemia This would imply therefore that this type of anemia in some unknown manner renders patients immune to various maladies and in others makes them more susceptible These are pituitary disorders diabetes thyroid disturbances carcinoma of the stomach tuberculosis

Diseases which Are Probably Related Etiologically to Pernicious Anemia—These conditions are such common complications that they may be considered as part of the syndrome (*Gallbladder disease* is such a frequent complication of pernicious anemia it is dealt with under a separate heading on page 303)

It is exceedingly common in my experience to see two types of *mental disturbances* with pernicious anemia which I believe may be attributed to the disease itself These are first a complete disorientation and delirium which is observed only in patients who have an exceedingly severe anemia and often a febrile reaction associated with it This condition usually disappears with treatment in a few days Before the days of effective treatment it would persist longer but even then it could be greatly improved by means of blood transfusions One could not resist speculating on the possibility that the immediate mechanism was an anoxemia of the brain due to the severe anemia

There is a second type of mental disturbance seen in this malady which consists of a mild irritability and depression It is observed at any time when the anemia is below 3 million cells per cubic millimeter I have the impression that this variety was more commonly encountered before effective treatment was available Hence the possibility was that mental change was one that was characteristically present in a patient with any *form of chronic disease* in which a fatal termination was inevitable At any rate this condition when now observed usually clears up entirely with the restoration of the blood to normal

In occasional instances I have observed the expansive over optimistic mental state of mind resembling that seen in general paresis to which Camp (*250*) directed attention as characteristic of pernicious anemia The first example ever seen by me in which this attitude of mind was conspicuous was presented many years ago in a clinic by the late Theodore Janeway The patient was a man of no mean business ability who had made an enviable success in life Upon developing pernicious anemia he became a *patient of Dr Janeway in the private* ward of the Johns Hopkins Hospital At his own suggestion he appeared before the students in the fourth year clinic where he put on a show which will long be remembered He gloried in his symptoms which he explained with great detail and pleasure and appeared to enjoy the presentation more than anyone else present That he was impressive is indicated by

the fact that after 30 years I can remember his gestures his remarks and the chief details about his impressive personal appearance

It is my opinion that the major psychoses are not a part of the syndrome of pernicious anemia This is because they are infrequently present and although they may improve with the disappearance of the anemia in many instances they do not The anemia in these cases should in most instances be regarded only as a precipitating cause It is important in this connection to note that Adams and Kubik (229) emphasize the occurrence of changes characteristic of subacute degeneration of the brain in some patients with pernicious anemia They do not think that every patient with pernicious anemia will have demonstrable brain lesions but it is their belief that all in whom there are definite and widely disseminated brain lesions will probably have mental disorders

Cystitis and in many instances an associated *pyelitis* is undoubtedly related to the commonly occurring changes in the spinal cord which result in the loss of the control of the sphincters of the bladder With this there is retention of urine stasis in the bladder and an inevitable infection As mentioned in the section on prognosis this is an important and often a persistent complication as the infection thus established prevents a complete hematological response to antipernicious anemia therapy The introduction in recent years of the sulfonamide drugs and antibiotic preparations has resulted in a much more favorable outlook when such a complication is present

Full details concerning the neurological complications of pernicious anemia have been discussed in the section devoted to them on page 284

Disease of the Gallbladder in Patients with Pernicious Anemia—It has long been known that disease of the gallbladder is not uncommon in patients with this disease One factor to account for this may be the constantly associated achlorhydria and the associated abnormal growth of *B coli* streptococci and *B welchii* at high levels in the intestinal tract Dick (251) has shown that a persistent achlorhydria tends to promote a growth of bacteria in the stomach similar to the flora of the colon Regardless of whether or not this plays a role gallbladder involvement is commonly encountered in patients with this disease Bethell and Harrington (252) found that 22 5 per cent of a group of our patients revealed abnormal gallbladder function by intravenous cholecystography The fact that gallbladder disease is frequently present in these patients is important from at least two standpoints namely (1) active infection may inhibit a satisfactory response to potent antipernicious anemia therapy and (2) it may be responsible for any gastrointestinal complaints which persist after a satisfactory therapeutic remission has been induced

Diseases Which Have a Fortuitous Association with Pernicious Anemia—These conditions are those which would be expected to be present

III Certain diseases about which there has been some discussion as to whether they occur in some instances with greater and in others with less incidence in patients with pernicious anemia This would imply therefore that this type of anemia in some unknown manner, renders patients immune to various maladies and in others makes them more susceptible These are pituitary disorders diabetes thyroid disturbances carcinoma of the stomach tuberculosis

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causal relationship In a group of 440 patients with pernicious anemia studied by Murphy and Howard (256) there were nine patients with the disease In Wilkinson's group (257) there were four patients with diabetes among the 370 who had pernicious anemia In most instances the diabetes usually develops after 40 years of age and consequently the diabetic condition is often mild

Pernicious Anemia and Diseases of the Thyroid Gland—Although a careful study of our patients has not been made in respect to the association of these two diseases it is my impression that there is no causal relationship between the two We have observed instances of exophthalmic goiter toxic adenoma and myxedema in patients with pernicious anemia but have been of the opinion that the association is merely fortuitous

The coexistence of exophthalmic goiter and pernicious anemia has been studied by Stenstam (258) who has given a complete review of the literature He found that between the years 1929 and 1938 in the clinic at Lund 28 414 patients were admitted Among these there were 389 with Basedow's disease and 192 with pernicious anemia In only three instances was there a combination of the two conditions in the same patient He concluded that the association should be considered incidental

The coexistence of either exophthalmic goiter or toxic adenoma with pernicious anemia is a highly undesirable one from the standpoint of pathologic physiology The elevated basal metabolic rate in either thyroid disorder means that an additional supply of oxygen associated with the increased heat production must be delivered to the tissues by the blood stream As the oxygen carrying capacity of the blood is directly proportional to its hemoglobin content it is obvious that in pernicious anemia the ability of the blood to transport oxygen from the lungs to the tissues may be greatly impaired in some cases of pernicious anemia This places an undue strain on the heart which must compensate for this by increasing the circulatory rate Such cases should be treated intensively with intramuscular liver extract 1 cc containing 15 units daily for several weeks or a comparable amount of vitamin B 12 and then three times weekly until the blood becomes normal It is also probably wise in such patients to give a number of blood transfusions in order to increase their red blood cell count rapidly When the blood has been returned to normal there is no reason why these patients should not undergo subtotal thyroidectomy or receive treatment with radioactive iodine as well as any other patient of the same age group

A number of patients have been reported in whom pernicious anemia and fully developed myxedema have coexisted (259) This association has been discussed in the section dealing with Differential Diagnosis (p 500) I have observed one such patient in whom the two condi

in persons of the age who develop pernicious anemia namely hypertension and atherosclerosis, cardiac disease cerebral vascular accidents and cancer of various organs but particularly the stomach

Some years ago I made a survey of the cause of death in 147 cases of pernicious anemia (253) It was found that rarely did the patients die of the anemia of pernicious anemia after effective antipernicious anemia therapy had been made available but almost always they succumbed to complications incident to the spinal cord changes or to some disease which is known to occur commonly at middle age or later The conditions, other than pernicious anemia which were the cause of death were as follows heart disease 11 cases cancer 11 cases hemiplegia seven cases, pneumonia five cases nephritis three cases accidents two cases pulmonary embolism two cases following surgical operations two cases hypertension one case cirrhosis of the liver one case, cyst of the brain one case septicemia one case acute appendicitis one case pulmonary tuberculosis one case

Heart disease occurred as a complication in 33 75 per cent of the 80 cases studied by Hardgrove and his associates (122) but they emphasize the fact that 30 per cent of their patients were over 70 years of age There was an incidence of 18 75 per cent of benign essential hypertension in their group

Pernicious Anemia and Pituitary Disease—Cases have been described in which hypopituitarism is associated with achlorhydria and anemia usually of the addisonian type (254) In the opinion of Witts (255) the presence of these two diseases in the same person is more than a coincidence According to him the occurrence of pernicious anemia with hyperthyroidism with pregnancy and pituitary disease suggests that there is a hormonal element or mechanism which may possibly lead to the degeneration of the cells responsible for the secretion of the intrinsic factor The fact that the incidence of pernicious anemia increases with advancing years in his opinion also suggests that the occurrence of pernicious anemia in a patient with hypopituitarism is another example of a precocious senile change to which the patient with pituitary disease is liable

The coexistence of these two diseases in the same patient has never been observed by me and the number of reported cases is small The burden of proof that this is more than a coincidental association is on those who claim otherwise In my opinion the most acceptable view which can now be held is that it is one of chance and furthermore that the possible relationship between the pituitary gland and the secretion of the intrinsic factor by the cells of the stomach mucosa is nothing more than one of interest from a speculative standpoint

Diabetes and Pernicious Anemia—These two disorders may be associated in the same patient but there is no indication that there is a

necropsies 641 had gastric cancer and 50 had pernicious anemia in 11 instances however gastric cancer was associated with pernicious anemia whereas the expected incidence of such an association on the basis of chance was only 2 4 cases

Other evidences in support of a causal relationship are the studies of Cotti (262) who found that in 107 patients with neoplasm associated with pernicious anemia 93 or 86 per cent of the tumors were located in the stomach Likewise Wilkinson (257) says that 70 per cent of all tumors in pernicious anemia were gastric and of all the patients who died of a malignant disease something under 30 per cent would be expected to die of gastric cancer

In summary Rhoads states "It appears likely that gastritis is associated with and probably precedes the development of certain cases of gastric cancer The association of pernicious anemia in which gastritis is always present with gastric cancer appears to be more frequent than could be explained by the laws of chance and furthermore there is some evidence that if one disorder is present in a family the other is likely to occur The occurrence of gastric cancer as a sequel of pernicious anemia is not infrequent and gastric polyposis is very much more common in pernicious anemia than in patients dead of other disorders"

A study bearing on this question has been made by Doehring and Eusterman (263) who reported the association of cancer of the stomach in 40 patients with pernicious anemia seen at the Mayo Clinic over a period of many years During the five year period from 1935 to 1939 inclusive 1014 patients with pernicious anemia were seen at the clinic Seventeen of these had carcinoma of the stomach which gives an incidence of 1 7 per cent According to them this seems slightly greater than the number of instances of gastric carcinoma among the general population

In a careful study of 301 patients with pernicious anemia over an average of 10 5 years Mosbech and Videbaek (264) found that eight females and seven males had died of carcinoma of the stomach whereas the expected incidence in a corresponding normal population would have been that 3 5 females and 1 7 males succumbed to this condition They conclude therefore that the number of patients dying from cancer of the stomach in their series exceeded the expected deaths and that the difference was significant for females as well as males

In a more recent article Kaplan and Rigler (265) present data which show that serial roentgenological and gastroscopic examinations of 259 patients with pernicious anemia demonstrated that 6 9 per cent had carcinoma of the stomach and 6 6 benign polyps making a total of 13 5 per cent with tumors of the stomach *They conclude that the two diseases are linked probably through the medium of some common factor Among the possible factors which they mention are hereditary and constitutional tendencies achlorhydria gastritis and liver therapy*

tions were undoubtedly present My patient a male age 60 had the classical features of myxedema and in addition an achlorhydria and a macrocytic anemia which was typical in all respects of pernicious anemia It was not possible to keep this patient in normal health unless both desiccated thyroid and antipernicious anemia medication were given simultaneously The occurrence of these conditions at the same time in the patient emphasizes two things One that they may coexist but probably only by chance and second that the anemia may influence the characteristically lowered basal metabolic rate in pernicious anemia I am not aware that this latter point has been emphasized in the literature It is known that the basal metabolic rate is elevated moderately in pernicious anemia when the anemia is severe (*260*) in myxedema of course the rate is constantly lowered often to a level between —30 and —40 When the two diseases co exist and the red blood cell count is in the vicinity of 1 0 to 1 5 millions per cubic millimeter the stimulating effect of the anemia on the basal metabolic rate is such that it overcomes *the lowered rate due to the lack of thyroid secretion Consequently* such a patient may show all of the striking clinical features of fully developed myxedema, and have a basal metabolic rate which is within normal limits As antipernicious anemia medication becomes effective however, and the anemia diminishes the rate will fall to —30 or lower, which is the level that the clinical picture would lead one to anticipate

Relationship between Pernicious Anemia and Cancer of the Stomach — With the increasing length of life in patients with pernicious anemia due to the effectiveness of antipernicious anemia therapy there has been a greater number of patients with the disease who developed cancer of the stomach in the surviving years in which the anemia of pernicious anemia has been controlled This coupled with the fact that previous instances of the simultaneous occurrences of the two diseases have been reported raises the question as to whether the changes in the gastric mucosa of a patient with pernicious anemia might not predispose a person to the development of a neoplastic lesion at that site

A very comprehensive survey of this question has been made by Rhoads (*261*) He first quotes from the studies of Brown (*220*) at the Boston City Hospital who found that chronic gastritis was present in 41 of 42 histologic studies of the stomach in patients dead of pernicious anemia He also observed that 8 per cent of these patients with pernicious anemia had benign gastric tumors whereas the incidence of such growths in patients dead of disorders other than pernicious anemia was 0 003 per cent It seems logical to conclude therefore that not only is gastritis regularly present in pernicious anemia but that it also predisposes to the development of polyps of the mucous membrane All agree moreover that gastric polyposis is a precancerous lesion

In support of the theory of a causal relationship between the two diseases Rhoads cites the figures of Rambach as follows of *11 849*

falls to 20 or 30 per cent of normal the blood has a low oxygen carrying capacity which might result in a failure to deliver the required amount of oxygen to the myocardium and hence anginal pain would occur

Certainly when a severe anemia is present the heart is required to do more work for it has been shown that with an anemia of 20 per cent the minute volume of blood circulated by the heart is increased 300 per cent and when the hemoglobin concentration is 50 per cent the circulatory rate returns to normal (266) Moreover in severe anemias there is a moderate increase in the basal metabolic rate which means that an added amount of oxygen must be delivered to the tissues and hence an increased amount of blood must be circulated This can only be accomplished by increasing the rate of circulation which adds an additional burden on the heart

Regardless of the considerations which would suggest to one that the two maladies might be associated frequently the reverse of this is true For example Giffin and Bowler (267) found that in 1560 cases of pernicious anemia that only 43 or 2.7 per cent also had symptoms of angina pectoris Only 1 per cent of 300 patients with pernicious anemia had angina pectoris in the group studied by Carter and Traut (268) Certainly the two conditions have not been commonly associated in my experience In the 2500 cases of pernicious anemia which have been observed at the Simpson Memorial Institute during the past 24 years angina pectoris has been known to occur in association with the disease but it has been seen rarely

It is my opinion that *anemia alone* cannot cause the symptoms of angina This is true if for no other reason than that it is rarely present in patients who have a pronounced reduction of the hemoglobin and red blood cell count It appears that there must be in addition some other factor such as a narrowing of the coronary arteries or possibly in some cases an aortic insufficiency with a low diastolic pressure This is the general belief of those who have studied the question Herrick (269) assumed that blood of poor quality going through somewhat narrowed coronary arteries might favor on slight provocation the development of an anginal attack This view is also taken by Levine who made the statement (270) that Even with one twelfth of the normal number of red blood cells I do not believe that the anemia would initiate an attack of angina without some background of coronary disease" Stalker (271) who has presented an admirable review of the literature and summarized the various views on this question likewise concludes that as most patients with pernicious anemia do not have angina the anemia per se cannot be the primary cause He believes however that when coronary stenosis exists and in addition the blood is deficient in oxygen-carrying power the functional capacity of the myocardium is impaired and angina occurs more readily

Tuberculosis and Pernicious Anemia —It is true that the infrequency of active pulmonary tuberculosis in patients with pernicious anemia is striking but no one to my knowledge has produced convincing evidence that it is any less common in these patients in accordance with the age and sex distribution than it is in the population at large *Certainly* it can occur as cases have been reported in the literature and one of our patients succumbed to it Furthermore in a group of 21 necropsies on our patients with *pernicious anemia definite evidence of tuberculosis* was found in about the ratio that is to be expected of this age group One patient age 68 years was found to have active tuberculosis of the bronchial *lymph glands at necropsy but this was not discovered* during life Five others had evidence of healed tuberculosis in the lungs bronchial lymph glands or the pleura and in one instance there was a *small encapsulated tubercle in the liver Six additional cases had old* adhesive pleuritis which in some instances might be interpreted as evidence of tuberculosis

It must be granted therefore that pulmonary tuberculosis may occur in patients with pernicious anemia and is occasionally the cause of death Furthermore evidence at necropsy suggests that the disease is present in about equal frequency in patients with pernicious anemia as it is in the population at large This conclusion is in accord with Wilkinson (257)

Pernicious Anemia and Skin Diseases —Comment is made by Wilkinson (257) on the association of skin disease and pernicious anemia In his group of 370 cases there were three of acne rosacea three of psoriasis vulgaris three of urticaria two of eczema one of leukoplakia and three of pruritus vulvae This author speculates on the possible relationship between acne psoriasis and urticaria and the achlorhydria It is emphasized by Murphy and Howard (256) that the incidence of vitiligo in their patients was greater than would be expected in a group of patients of similar age who did not have pernicious anemia They state although the presence of vitiligo has been associated with achylia gastrica it seems more likely that it is another manifestation of a nutritional disturbance of a deficiency which may be fundamentally important in the production of pernicious anemia

Angina Pectoris and Pernicious Anemia —Cases of pernicious anemia accompanied by angina pectoris have been reported and it is remarkable that the association is not more commonly encountered because the age incidence of the two conditions is approximately the same Furthermore if the present day theory of anginal pain is accepted namely that it is due to anoxia of the myocardium then it would be expected that an anemia would contribute to this situation This is because the oxygen carrying capacity of the circulating blood is directly proportional to the amount of hemoglobin contained in it Hence when the *hemoglobin*

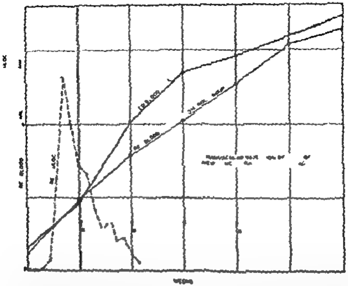

Fig 31 —Figure to show the characteristic changes which occur in the peripheral blood of a patient with pernicious anemia when effective treatment is given In this case the therapy employed was a highly potent liver extract which was given intramuscularly Essentially the same changes would occur when any type of antipernicious anemia medication is employed provided a sufficient dosage is used The earliest evidence of improvement occurs between the first and third days as an increase in the number of reticulocytes from an average of below one per cent before treatment to a maximum number on the fourth to the eighth days and a return to normal on about the fourteenth day of treatment The height of the curve is inversely proportional to the level of the red blood cell count prior to treatment (see Table XIX) When this characteristic reticulocyte response occurs then it can be anticipated that the red blood cells will *increase* in number at the rate of between 200 000 and 400 000 *per* cubic millimeter per week In the above case the erythrocyte increase was somewhat better than average as it was 500 000 per cubic millimeter per week (Bethell courtesy *New York State Journal of Medicine*)

Treatment with Refined Liver Extract —A long experience has shown that in general refined liver extract is a satisfactory form of treatment In a few patients as will be discussed later it appears to be necessary to augment the treatment with folic acid in order to cause the red blood cell count to attain a high normal level and remain there

Apparently the potency of liver extract is chiefly if not entirely dependent of its vitamin B_{12} content Furthermore it is a reasonable assumption to state that in general one unit of liver extract which is the daily amount necessary to induce a remission is roughly equivalent to 1 microgram of vitamin B_{12} This cannot be accepted as a precise relationship as indicated by the studies of Meacham and his associates (272) but it serves as a useful approximation

Preparations of liver extract are commercially available for intramuscular injections in strengths of 1 2 2.5 3.3 4 5 10 and 15 units per cubic centimeter Some have claimed advantages for the crude or more dilute preparations especially in the treatment of patients who have

The various factors which are concerned with the relationship of anemia to angina pectoris are well shown in a patient whom I had under my observation The patient a male 62 years of age had a myelogenous leukemia with a moderately severe anemia About one year before I saw him for a short time he had the symptoms of angina pectoris which appeared only on exertion Shortly after this the characteristic features of myelogenous leukemia appeared including an anemia with the hemoglobin in the vicinity of 50 per cent With this his activities were very much curtailed on account of weakness and the attacks of precordial pain were no longer observed Some time later however the hemoglobin of the circulating blood decreased to 30 per cent and the basal metabolic rate rose to 45 per cent At this time, the attacks of precordial pain reappeared even though he rarely exerted himself physically The attacks usually came on immediately following meals With repeated transfusions and a rise in the hemoglobin to over 50 per cent the attacks ceased In my opinion this man undoubtedly has narrowing of the coronary arteries but when the hemoglobin of the blood was 50 per cent or more sufficient oxygen reached the myocardium to supply its needs With the development of a severe anemia and in addition increased demands due to the acceleration of the basal metabolic rate and the ingestion of food then the amount of oxygen delivered to the myocardium was inadequate and an anoxia of the myocardium resulted with anginal pain

TREATMENT

The most important aspect of the treatment of pernicious anemia is the administration of an adequate amount of potent antipernicious anemia medication which will cause the blood to increase from the anemia level to normal in the shortest period of time and subsequently maintain it *completely* within normal limits

Types of Specific Antipernicious Anemia Medication—There are three preparations which should be given consideration namely (1) refined liver extract which apparently depends chiefly if not entirely on its vitamin B_1 content for potency (2) vitamin B_1 which appears to be equally effective as refined liver extract and may eventually supplant it (3) folic acid for oral or parenteral use which is not recommended as a sole form of therapy in patients with pernicious anemia as *it does not affect the neurological changes favorably* and (4) a combination of vitamin B_{12} injections intramuscularly and folic acid orally both of which are probably essential for the efficient treatment of occasional patients with the disease

Oral therapy with liver extract stomach preparations folic acid alone and vitamin B_1 are not recommended as preferred forms of treatment their effectiveness is discussed on page 322

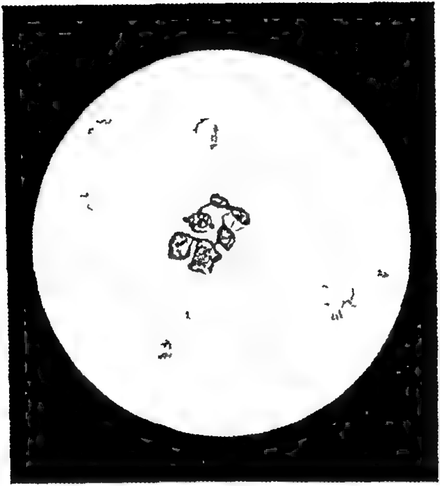

PLATE III *Pernicious Anemia*—Early reticulocytosis induced by specific therapy. Erythrocyte count before treatment was 1 200 000 per cubic millimeter. On the fourth day after the intramuscular injection of liver extract 15 units U.S.P. the reticulocyte percentage was 16. Abnormalities in size and shape of the red blood cells are still conspicuous and large neutrophils with hypersegmentation of the nuclei are present but the serum bilirubin and urine urobilinogen had decreased to nearly normal levels and clinical improvement was evidenced by increased appetite and sense of well being. Two days later the percentage of reticulocytes reached a maximum of 45. Subsequently it declined within a period of two weeks to less than 3 although treatment with liver extract was continued. The erythrocyte count progressively increased and exceeded 4 500 000 per cubic millimeter five weeks after the institution of specific therapy. Wright's stain. Magnification 960

TABLE XIX

THE EXPECTED MAXIMUM RETICULOCYTE PERCENTAGE AFTER DIFFERENT MODES OF TREATMENT IN PERNICIOUS ANEMIA WITH VARIOUS INITIAL RED BLOOD CELL COUNTS

Desiccated Stomach 40 Gm Daily			*Liver Extract Oral 18 Gm Daily*			*Liver Extract Intravenous Single Dose 10 Units*			*Liver Extract Intramuscular Daily 1–2 Units*		
(R B C)		(R %)	(R B C)		(R %)	(R B C)		(R %)	(R B C)		(R %)
0.5	=	61.2	0.5	=	55.7	0.5	=	66.1	0.5	=	56.8
0.6	=	56.6	0.6	=	50.4	0.6	=	61.8	0.6	=	52.9
0.7	=	52.5	0.7	=	45.7	0.7	=	57.8	0.7	=	49.3
0.8	=	48.7	0.8	=	41.6	0.8	=	54.1	0.8	=	46.0
0.9	=	45.1	0.9	=	38.0	0.9	=	50.6	0.9	=	42.9
1.0	=	41.8	1.0	=	34.6	1.0	=	47.4	1.0	=	40.0
1.1	=	38.8	1.1	=	31.7	1.1	=	44.3	1.1	=	37.3
1.2	=	36.0	1.2	=	29.0	1.2	=	41.5	1.2	=	34.8
1.3	=	33.2	1.3	=	26.5	1.3	=	38.8	1.3	=	32.4
1.4	=	30.8	1.4	=	24.3	1.4	=	36.2	1.4	=	30.1
1.5	=	28.4	1.5	=	22.3	1.5	=	33.8	1.5	=	28.0
1.6	=	26.2	1.6	=	20.4	1.6	=	31.5	1.6	=	26.0
1.7	=	24.2	1.7	=	18.7	1.7	=	29.4	1.7	=	24.1
1.8	=	22.2	1.8	=	17.1	1.8	=	27.3	1.8	=	22.3
1.9	=	20.3	1.9	=	15.6	1.9	=	25.4	1.9	=	20.6
2.0	=	18.6	2.0	=	14.1	2.0	=	23.5	2.0	=	19.0
2.1	=	16.9	2.1	=	12.9	2.1	=	21.8	2.1	=	17.5
2.2	=	15.4	2.2	=	11.6	2.2	=	20.1	2.2	=	16.0
2.3	=	13.9	2.3	=	10.5	2.3	=	18.5	2.3	=	14.5
2.4	=	12.4	2.4	=	9.4	2.4	=	16.9	2.4	=	13.3
2.5	=	11.1	2.5	=	8.4	2.5	=	15.5	2.5	=	12.0
2.6	=	9.8	2.6	=	7.5	2.6	=	14.1	2.6	=	10.8
2.7	=	8.5	2.7	=	6.6	2.7	=	12.7	2.7	=	9.6
2.8	=	7.3	2.8	=	5.7	2.8	=	11.4	2.8	=	8.5
2.9	=	6.2	2.9	=	4.9	2.9	=	10.2	2.9	=	7.4
3.0	=	5.1	3.0	=	4.1	3.0	=	9.0	3.0	=	6.4
3.1	=	4.1	3.1	=	3.4	3.1	=	7.8	3.1	=	5.4
3.2	=	3.1	3.2	=	2.7	3.2	=	6.7	3.2	=	4.5
3.3	=	2.2	3.3	=	2.1	3.3	=	5.3	3.3	=	3.5
3.4	=	1.2	3.4	=	1.5	3.4	=	4.6	3.4	=	2.7
3.5	=	0.3	3.5	=	0.9	3.5	=	3.6	3.5	=	1.8

TABLE XIX —Table indicating the maximum reticulocyte count on the fourth to the sixth day in patients with pernicious anemia when the various antipernicious anemia medications are given in the doses indicated The response of the reticulocytes when considered with the increase in the red blood cell count is a valuable method of assaying the potency of various substances employed in the treatment of pernicious anemia It will be noted that there is an inverse ratio between the reticulocyte response and the level of the red blood cell count prior to treatment in other words the lower the initial red blood cell count the higher the anticipated reticulocyte response If the anticipated reticulocyte response as shown above is not attained then one should consider that (1) the diagnosis of pernicious anemia may be in correct (2) the material is not of full potency (3) the patient may have some active infection which inhibits the antipernicious anemia activity of the preparation (4) the patient is of such an advanced age (usually over 65 years) that an increased amount of medication is necessary to produce the expected reticulocyte rise

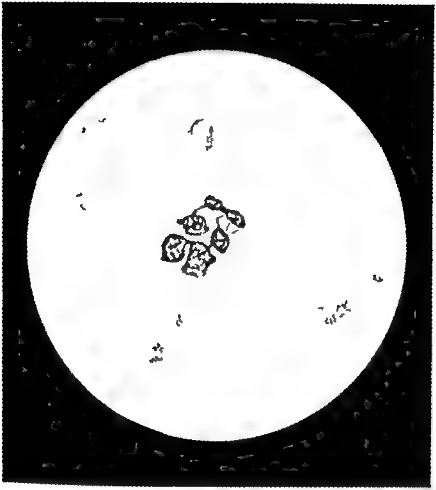

PLATE III *Pernicious Anemia*—Early reticulocytosis induced by specific therapy Erythrocyte count before treatment was 1 200 000 per cubic millimeter On the fourth day after the intramuscular injection of liver extract 15 units U.S.P the reticulocyte percentage was 16 Abnormalities in size and shape of the red blood cells are still conspicuous and large neutrophils with hypersegmentation of the nuclei are present but the serum bilirubin and urine urobilinogen had decreased to nearly normal levels and clinical improvement was evidenced by increased appetite and sense of well being Two days later the percentage of reticulocytes reached a maximum of 45 Subsequently it declined within a period of two weeks to less than 3 although treatment with liver extract was continued The erythrocyte count progressively increased and exceeded 4 500 000 per cubic millimeter [illegible] weeks after the institution of specific therapy Wright's stain Magnification 960

nervous system a return to a fairly normal existence and activities of life may be possible within eight to 12 weeks It is to be expected however that the often associated paraethesis will persist for a much longer time

The earliest evidence of a remission in the circulating blood is an increase in the young red blood cells or reticulocytes which usually begins within 36 to 48 hours after parenteral therapy has been instituted and within three to six days after oral medication Ordinarily the reticulocytes in the blood of a patient in relapse number approximately 1 per cent or less Coincident with the evidence of clinical improvement they begin to increase in numbers until a peak is reached on the fourth to the sixth day when parenteral therapy is used and somewhat later with oral therapy The curve of the reticulocyte increase usually returns to the normal level of 1 per cent or less on about the fifteenth day after treatment has been initiated

The peak of the curve indicating the number of reticulocytes in the blood bears an accurate inverse relationship to the level of the red blood cell count before treatment was instituted As this maximum level of the reticulocytes varies with the types of medication administered it can be utilized to assay various antipernicious anemia preparations for potency Table XIX shows the maximum reticulocyte responses in patients with pernicious anemia following the administration of the various types of liver and desiccated stomach therapy

The optimum response to antipernicious anemia therapy is also indicated by an increase in the red blood cell count averaging between 300 000 and 500 000 per cubic millimeter per week Usually it is best to determine the count after a period of 14 days as the rise during the first week may not be great but the striking improvement which occurs in the second week may easily bring the increase up to a satisfactory average for the two week period

In a study of data from 523 patients at the Simpson Memorial Institute Riddle (276) found that the average weekly increase in the erythrocyte count at the end of two weeks of treatment had an inverse relationship to the erythrocyte count before treatment This relationship could be expressed in the equation $I = 0.78 - 0.174\ Eo$ where I is the average weekly increase in the erythrocyte count after two weeks of treatment and Eo the erythrocyte count before treatment expressed as millions of erythrocytes per cubic centimeter of blood The following table slightly modified from the one prepared by Riddle indicates what is considered to be adequate responses in the red blood cell count to effective therapy in accordance with this formula

Figure 34 (277) shows the average rate of formation of red blood cells after intramuscular liver therapy given in a dosage of one to two units daily in terms of weekly changes for each initial count From the general slope of these lines the red blood cell count per cubic millimeter is indicated at weekly intervals from one to eight weeks If the rate

continues to increase uniformly a red blood cell count of 5.0 million per cubic millimeter may be expected in any given patient at the end of eight weeks regardless of the level of the initial count Many factors

TABLE XX

Red Blood Cell Count Before Treatment (Millions per Cubic Millimeter)	*Average Weekly Increase Based upon the First Two Weeks of Treatment (Millions per Cubic Millimeter)*
0.5	0.693
0.6	0.676
0.7	0.658
0.8	0.641
0.9	0.623
1.0	0.606
1.1	0.589
1.2	0.571
1.3	0.554
1.4	0.536
1.5	0.519
1.6	0.502
1.7	0.484
1.8	0.467
1.9	0.449
2.0	0.432
2.1	0.415
2.2	0.397
2.3	0.380
2.4	0.362
2.5	0.345
2.6	0.328
2.7	0.310
2.8	0.293
2.9	0.275
3.0	0.258
3.1	0.241
3.2	0.223
3.3	0.206
3.4	0.188
3.5	0.171
3.6	0.154
3.7	0.136
3.8	0.119
3.9	0.101
4.0	0.084
4.1	0.067
4.2	0.049
4.3	0.032
4.4	0.014

(Riddle Courtesy *American Journal of the Medical Sciences*)

as infection iron deficiency and an abnormal rate of blood destruction and possibly advanced arteriosclerosis may modify this The relationship between the initial red blood cell count and the maximum reticulo

cyte response has been found to be a fairly precise one which is of value in assaying the potency of various antipernicious anemia preparations Riddle (278) found that the formula $R = \frac{0.73 - 0.2\ Eo}{0.73 + 0.8\ Eo}$ obtained by combining the two equations of Minot and Cohn $EpR = \frac{EoR}{I - R} - 0.73 - 0.2\ Eo$ was reasonably accurate in predicting the magnitude of the reticulocyte percentage response in cases treated with the usual dose of liver extract daily Similar curves have been devised by Bethell and Goldhamer (279) for the maximum reticulocyte values following ventriculin and intravenous liver extract therapy

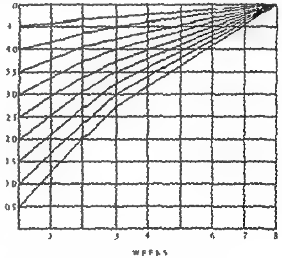

Fig 34—Figure showing the red blood cell rise in 129 patients treated daily with 1 to 2 units of liver extract intramuscularly Although the rate of increase is more rapid in the first weeks of treatment in patients with a low initial red blood cell count it should be noted that regardless of the level of the red blood cell count when treatment is begun a final count of 5 million per cubic millimeter is reached at the end of eight weeks in all patients (*Isaacs et al courtesy Journal of the American Medical Association*)

From our experience over a period of 26 years at the Simpson Institute the maximum reticulocyte response has been calculated for all types of therapy and utilized along with the increase in the red blood cell count in the evaluation of the potency of various antipernicious anemia preparations (These criteria in terms of the maximum reticulocyte percentages for the various types of antipernicious anemia therapy are given in Table XX)

Maintenance Dose of Intramuscular Liver Extract —After the red blood cell count has reached normal limits it should be impressed upon the patient that *it will be necessary to continue taking some type of anti*pernicious therapy at regular intervals continuously for an indefinite

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Eo represents the erythrocyte count at the beginning of treatment Ep the erythrocyte count at time of maximum reticulocyte response and R the maximum percentage of reticulocytes I represents the average weekly increase in the erythrocyte count during the first two weeks of treatment

period regardless of a disappearance of all symptoms The precise minimum amount of liver extract which is necessary to maintain the blood with the limits of normal varies with different individuals but the matter is so important that no risk of a subminimal dosage should be taken I prefer, in most instances to give an injection of 1 cc containing 15 units every two weeks, although some recommend that the interval between doses can be lengthened As there is so much at stake, for with inadequate dosage the neural manifestations may progress an excess of medication is preferable which does no harm rather than an effort to space the treatments at the greatest possible interval for then the red blood cell count may fall below normal

Strauss Solomon and Fox (*280*) state what they consider to be reliable criteria of adequate therapy and I am in complete accord with their suggestions They are as follows first the red blood cell count should be 4 5 million per cubic millimeter or higher, and the mean corpuscular volume within normal limits second there must be no symptoms of any nature such as glossitis or indigestion attributable to pernicious anemia third and the most important if there should be a recurrence of persistent numbness tingling or other paraesthesia of the extremities the dose of liver extract should be doubled fourth if the patient presents any other subjective manifestations which might be considered as due to a progression of the spinal cord lesions this is also an indication to double the dose It should also be added here that any type of infection even a mild cold calls for a double amount of medication during the period of the disability An additional precaution is that older patients in general require more therapy than do patients under 50 years of age

Vitamin B_{12} in the Treatment of Pernicious Anemia —This vitamin was discovered in May of 1947 by Mary Shorb (*281*) who later showed that there was a linear relationship between the vitamin B_{12} content of different liver extracts and their effectiveness in the treatment of pernicious anemia This led West (*282*) in 1948 to test the action of crystalline vitamin B_{12} when given intramuscularly to patients with pernicious anemia

At approximately the same time in England E Lester Smith (*283*) working independently isolated by partition chromatography two red pigments from beef liver which were likewise shown by Ungley (*284*) to be highly potent when administered intramuscularly to patients with pernicious anemia Hence two investigators working independently and employing different methods discovered the antipernicious anemia vitamin B_{12} the latest component of the vitamin B complex Since these initial observations (*285 286 287 288 289 290 291 292 293*) numerous observers have concluded that the injection of this vitamin in patients with addisonian pernicious anemia will produce a hematological response similar to that produced by highly potent liver extract

All observers are in accord with the statement that either the crystalline vitamin B_{12} or the concentrate when given parenterally is an effective substitute for liver extract in the treatment of pernicious anemia and that it affects favorably the hemopoietic gastrointestinal and neurological manifestations of the disease (283) It is therefore a complete treatment of the disease Although all evidence indicates that vitamin B_{12} is equal in effectiveness to refined liver extract there is nothing to indicate that it produces superior results It is useful to replace liver extract when the patient becomes sensitive to this preparation and it is possible vitamin B_{12} medication may eventually become somewhat less expensive although this is not an important item at present

Dosage of Vitamin B_{12} —A patient in relapse should receive 10 to 15 micrograms intramuscularly of the vitamin daily for the first week the same amount three times weekly for the second and third weeks and twice weekly thereafter until the red blood cells reach 4 5 to 5 0 millions per cubic millimeter A maintenance dose is from 15 to 20 micrograms every two weeks It is probable that further experience will indicate that doubling this dose and giving it every four weeks will maintain the blood in a satisfactory condition

It has been assumed that approximately 1 microgram of vitamin B_{12} is equivalent in its effect to 1 U S P antipernicious anemia unit of liver extract (292) More recently in a study of 30 patients with pernicious anemia who were treated with this vitamin it is concluded by Meacham *et al* (272) that this assumption will provide an inadequate amount as maintenance dosage as 20 of the 30 patients whom they treated on this basis at the end of the treatment period had erythrocyte counts under 4 0 millions per cubic millimeter although no neurologic or lingual relapses were observed These observations emphasize therefore that the exact dosage in any given patient can only be determined by examining the blood at frequent intervals and adjusting the dosage until it is sufficient to keep the erythrocyte level at 4 5 or 5 0 millions per cubic millimeter

It has been concluded by Reisner and Weiner (293) that massive 1000 microgram single injections of vitamin B_{12} cannot be substituted efficiently for regular injections of smaller doses at more frequent intervals When such large doses are employed at widely separated intervals the observers believe that there is a danger of relapse and aggravation of central nervous system disease Furthermore they have concluded that massive weekly doses of vitamin B_{12} are not superior to the injection to the regular conventional doses *In their opinion this is because amounts of vitamin B_{12} above a threshold value of 25 to 50 micrograms by injection are rapidly and quantitatively excreted in the urine*

Among the recommendations made by the Anti Anemia Preparations Advisory Board (294) it is stated that (1) so far as the treatment of pernicious anemia is concerned liver injection U S P and liver injection

(crude) U S P are solutions of vitamin B_{12} (2) that there is no advantage in employing liver injection U S P or vitamin B_{12} injection U S P which contains more than 20 micrograms of vitamin B_{12} activity per cubic centimeter because of the great urinary loss when larger doses are injected (3) *vitamin B_{12} like purified liver extract, when given by injection* is usually many (perhaps 60 to 100) times as active as when given orally and (4) although there is some difference of opinion, the maintenance treatment of uncomplicated cases of pernicious anemia may be satisfactorily accomplished by injections at intervals of not longer than one month of either liver injection U S P or vitamin B_{12} U S P in such amounts that the patient will receive an average of at least 1 microgram of vitamin B_{12} daily

The Value of Folic Acid (Pteroylglutamic Acid) in the Treatment of Pernicious Anemia —The daily administration of 10 to 20 milligrams of folic acid either orally, intramuscularly, or intravenously will produce a prompt and satisfactory reticulocyte rise and a standard increase in the hemoglobin and red blood cells of the circulating blood in patients with pernicious anemia and other types of macrocytic anemia with a megaloblastic bone marrow *(77 78, 79 81 82 83A)* *Furthermore* many patients who had previously had the red blood cell count maintained within normal limits for a considerable period of time by means of liver extract intramuscularly will not have *a decrease* in hematological values when folic acid in doses of 10 to 15 milligrams are substituted for liver therapy In some patients but not all a daily dose as small as 5 milligrams orally will serve satisfactorily for maintenance purposes

The Risk of Folic Acid in the Treatment of Pernicious Anemia —Soon after folic acid was introduced into clinical medicine however as a form of treatment of patients with pernicious anemia it became apparent that its use involved a serious risk This was that during treatment with the drug *although the red blood cell count increased satisfactorily and the* patient developed complete hematological remission there might at the same time be serious progression of the neurological manifestations of the disease This occurred in two patients under my observation and was also the subject of a report by Vilter Vilter and Spies *(84)* In 21 patients with pernicious anemia who were treated with 70 to 105 milligrams of folic acid orally per week for a period of 10 to 12 months paraesthesia in the extremities and an unsteady gait developed in four of their patients within a period of five to eight months Neurological signs appeared and progressed until there were outspoken evidences of combined system disease present These observers conclude that folic acid when given *orally in divided doses of 70 to 105 milligrams* per week will maintain patients with pernicious anemia and sprue in a normal hematological state but *will not prevent the occurrence of degenerative disease of the spinal cord and peripheral nerves in patients with pernicious anemia*

Observations by Ross Belding and Paegel (295) on 21 patients with pernicious anemia who were receiving folic acid therapy alone for periods ranging from eight to 17 months likewise demonstrate the ineffectiveness of this preparation in controlling the neurological manifestations of this disorder In 11 of these patients subacute combined degeneration of the spinal cord either developed or if present showed progression during folic acid treatment In most instances this occurred when the peripheral blood was normal

More recently Schwartz Kaplan and Armstrong (296) have reported on a comprehensive study of the therapeutic effectiveness of folic acid and have likewise concluded that it is an unsatisfactory form of maintenance treatment of pernicious anemia They studied 98 patients over a three and one half year period in order to evaluate the therapeutic effectiveness of 5 milligrams daily of this preparation Twenty three of the patients relapsed hematologically half in less and half in more than two years and the same number relapsed neurologically all in less than two years Nine patients had combined neurological and hematological relapses It is of interest to note from a prognostic standpoint that all of the relapses both hematological and neurological were reversible with intensive liver extract therapy Only 12 patients were satisfactorily maintained on folic acid during the study period

These results reemphasize obviously that folic acid alone has no place in the treatment of patients with pernicious anemia although it is likely that more satisfactory results would have been accomplished if the daily dose of folic acid had been larger than 5 milligrams

It should be kept in mind however that although folic acid in some patients with pernicious anemia will not benefit the neurological manifestations and therefore *should not be used as a sole form of treatment in this disease* there is no proof that moderate doses of folic acid when combined with liver extract or vitamin B_{12} therapy will influence the nervous system changes adversely Furthermore it has been demonstrated that folic acid is effective in practically all other types of macrocytic anemia with megaloblastic bone marrow and in such patients it does not cause neurological changes (297 298) In addition it has been shown by Harvey Howard and Murphy (299) that folic acid in daily doses of 20 milligrams for three to 12 months in 40 subjects without pernicious anemia had no toxic effects on the central nervous system

Folic acid is therapeutically effective in patients with sprue the macrocytic anemia of pregnancy nutritional anemia the megaloblastic anemia of infancy dibothriocephalus latus infestation and the macrocytic anemia associated with liver disease intestinal anastomosis and stenosis total gastrectomy coeliac disease and idiopathic steatorrhea

Treatment with a Combination of Liver Extract or Vitamin B_{12} and Folic Acid—While folic acid should *never* be employed as the sole replacement therapy in pernicious anemia there is reason to believe that

(crude) U S P are solutions of vitamin B_{12} (2) that there is no advantage in employing liver injection U S P or vitamin B_{12} injection U S P which contains more than 20 micrograms of vitamin B_{12} activity per cubic centimeter because of the great urinary loss when larger doses are injected (3) vitamin B_{12} like purified liver extract, when given by injection is usually many (perhaps 60 to 100) times as active as when given orally, and (4) although there is some difference of opinion, the maintenance treatment of uncomplicated cases of pernicious anemia may be satisfactorily accomplished by injections at intervals of not longer than one month of either liver injection U S P or vitamin B_{12} U S P in such amounts that the patient will receive an average of at least 1 microgram of vitamin B_{12} daily

The Value of Folic Acid (Pteroylglutamic Acid) in the Treatment of Pernicious Anemia—The daily administration of 10 to 20 milligrams of folic acid either orally intramuscularly or intravenously will produce a prompt and satisfactory reticulocyte rise and a standard increase in the hemoglobin and red blood cells of the circulating blood in patients with pernicious anemia and other types of macrocytic anemia with a megaloblastic bone marrow (*77 78 79 81 82 83A*) Furthermore many patients who had previously had the red blood cell count maintained within normal limits for a considerable period of time by means of liver extract intramuscularly will not have a decrease in hematological values when folic acid in doses of 10 to 15 milligrams are substituted for liver therapy In some patients but not all a daily dose as small as 5 milligrams orally will serve satisfactorily for maintenance purposes

The Risk of Folic Acid in the Treatment of Pernicious Anemia—Soon after folic acid was introduced into clinical medicine however as a form of treatment of patients with pernicious anemia it became apparent that its use involved a serious risk This was that during treatment with the drug although the red blood cell count increased satisfactorily and the patient developed complete hematological remission there might at the same time be serious progression of the neurological manifestations of the disease This occurred in two patients under my observation and was also the subject of a report by Vilter Vilter and Spies (*84*) In 21 patients with pernicious anemia who were treated with 70 to 105 milligrams of folic acid orally per week for a period of 10 to 12 months paraesthesia in the extremities and an unsteady gait developed in four of their patients within a period of five to eight months Neurological signs appeared and progressed until there were outspoken evidences of combined system disease present These observers conclude that folic acid when given orally in divided doses of 70 to 105 milligrams per week will maintain patients with pernicious anemia and sprue in a normal hematological state but *will not prevent the occurrence of degenerative disease of the spinal cord and peripheral nerves in patients with pernicious anemia*

Before liver extract for parenteral use became available it was useful in some instances in which patients with pernicious anemia were semi comatose to give raw liver suspended in water by stomach tube This could be continued until the patient improved so swallowing was possible and cooked liver could be ingested

At present a liver extract powder for oral use is available and may be used in the treatment of patients who are allergic to liver extract intramuscularly or those who are so located that it is not feasible to give intramuscular injections It may be given in doses of 12 75 grams (three level teaspoonfuls) daily which represents one official unit In my opinion however it is a poor substitute for parenteral therapy and should never be employed except under the most unusual circumstances

Ventriculin or desiccated defatted hogs stomach is effective in the treatment of pernicious anemia provided only certified products are used This should be administered suspended in water in a dosage of 40 grams daily until the blood reaches normal then in doses varying from 20 to 30 grams daily in order to maintain the blood at a normal level

Another form of medication for oral use which is effective is Extralin a stomach liver concentrate It should be given as a maintenance dose in the form of four pulvules (2 grams) three times daily

The use of a proteolyzed liver preparation of oral use has been advocated by Davis and Davidson (*302*) This is prepared by the action of the enzyme papain on mammalian liver These observers suggest that a product thus made might be low in cost and that it might be useful in treating patients who could not arrange for regular injections of liver extract They also express the opinion that it might be extremely useful in the treatment of refractory anemias including the idiopathic type and also the anemias in association with pregnancy and the puerperium and those present in nutritional disorders such as sprue

The Oral Administration of Vitamin B_{12}—From a practical therapeutic standpoint vitamin B_{12} should not be administered orally as apparently its absorption is uncertain When the vitamin has been given orally in combination with normal gastric juice (*303*) and with an extract of hog duodenum (*304*) an adequate hematological response has followed Such studies serve as a basis for the development of a possible potent oral preparation in the future

It has been reported by Spies and his associates (*305*) that by giving as high as 900 micrograms daily of vitamin B_{12} for 20 to 27 days without the addition of intrinsic factor some favorable effects have been noted More recently Ungley (*306*) has reported that there is probably some inefficient absorption of the vitamin when it is given orally In a study of 7 patients with pernicious anemia Meyer and his associates (*307*) have reported substandard results following the administration of 75 to 300 micrograms daily to seven patients with pernicious anemia

some patients derive added benefit from the use of this drug when it is given orally in combination with standard doses of concentrated liver extract or vitamin B_{12} intramuscularly In an occasional patient it does not appear to be possible to cause the red blood cell count and hemoglobin percentage of the circulating blood to reach normal limits with liver or vitamin B_{12} therapy alone For example it is recorded by Jones Tillman and Darby (*300*) that one of their patients with pernicious anemia who had been receiving 50 units of liver extract parenterally every two weeks over a period of three years had a red blood cell count which was always 4 0 million per cubic millimeter or less Such patients should be given 5 to 10 milligram doses daily of folic acid orally as supplementary medication Spies (*301*) reports a study of 10 elderly patients with pernicious anemia in whom the red blood cell counts were below 4 0 million per cubic millimeter and in whom no improvement followed the administration of 150 to 250 micrograms of vitamin B_{12} over a period of 6 weeks While the dosage of vitamin B_{12} was then kept constant folic acid therapy was added In all of the patients the blood levels then increased to a normal level and their general health improved

It is my belief therefore, that folic acid should be added to the therapy of patients with pernicious anemia who are receiving liver extract or vitamin B_{12} if it is not possible to cause an increase in their blood to normal with liver extract or vitamin B_{12} alone Furthermore I do not believe that the addition of folic acid under these circumstances will exert an unfavorable effect on the neurological manifestations

The Treatment of Pernicious Anemia with Preparations Given Orally —Although oral preparations are effective in the treatment of pernicious anemia they are much less efficient than the intramuscular injection of liver extract or vitamin B_{12} *Hence they should never be employed routinely as the treatment of choice*

When liver was first introduced in the treatment of pernicious anemia in 1926 it was usually given in the form of cooked calf's liver in amounts of one half pound daily This was continued until the red blood cell count reached normal A maintenance dose was then employed which varied somewhat with the individual patient but it usually consisted of one quarter pound of cooked liver four or five times weekly I had under my observation a patient whom I treated for pernicious anemia for an interval of 18 years during which time his sole form of therapy was cooked liver Frequent blood counts during this period showed that the blood once having reached normal always remained so and the patient continued in perfect health Despite our urging the patient steadfastly refused to take any other forms of antipernicious anemia medication than cooked liver from the beginning of treatment and it proved to be most effective in his case There are few patients however who could continue with this type of therapy for such a long period of time

occurred locally after a test dose with as minute an amount as 0 1 cc of a 1 1000 dilution intracutaneously On the other hand it has been known that a patient may have a reaction when 1 cc of reticulogen is given subcutaneously whereas this effect does not follow the injection of 0 5 cc given in the same manner Reactions most commonly occur after the product has been well tolerated for weeks months or even years and especially after a long interval between the injections The authors recognize the very remarkable and unexplained fact that although the patient may have the initial reaction after numerous injections it may disappear for no apparent reason and never occur again despite a continuation of the same type of medication The suggestion is made that these reactions may be due occasionally to inadvertent intravenous injections Sensitivity to liver extract may persist for a long period of time even up to eight years in one patient The authors report that in the 61 cases of reactions to liver extract reported in the literature only six are stated to have definite evidence of allergy 13 showed no other allergic manifestations and in the remainder no statement was made The clinical manifestations of the reactions to liver extract are exceedingly diverse The most frequently encountered is either urticaria alone or in association with other allergic symptoms The most common types are purely local reactions with pain edema erythema and itching On the other hand the reactions may be severe as evidenced by the characteristic features of angioneurotic edema or asthma In some cases the manifestations of typical anaphylactic shock appear such as weakness a rapid and weak pulse vomiting dyspnea urticaria and a pronounced fall in blood pressure The authors state that almost the whole gamut of allergic manifestations have been described They report that no fatalities have occurred although I can state that in some cases the symptoms are so severe as to suggest the possibility of an imminent fatality and one fatal case has been observed in England (309)

Of interest are the results of the intracutaneous test performed with various brands of liver extract which appear in the literature The total number of patients who have had allergic reactions from liver extract who were subsequently tested intracutaneously numbered 26 of whom 24 showed positive skin tests Of 11 patients studied by Kaufman and his associates eight showed positive tests It is generally agreed that the cause of a large majority of the reactions following the oral or parenteral administration of liver extract undoubtedly is related to allergy This opinion is supported by the clinical picture the positive intradermal tests and the reported presence of reagins and precipitins in a few patients It is of interest to note that if the patients are allergic to some substance in the liver extract it is a sensitivity to the organ and not to the animal species For example if a patient reacts to beef liver it is likely that swine or sheep liver will produce the same effect It seems

While the above studies are of importance from a theoretical standpoint, they indicate clearly that when the vitamin is given alone even in large doses the therapeutic results are too uncertain for this route of administration to be employed in practice

Allergy to Intramuscular Injections of Liver Extract —Ordinarily patients can take the necessary maintenance dose of liver extract at regular intervals for a period of years without untoward symptoms In an occasional instance however certain symptoms apparently on an allergic basis will develop which usually require that some change be made in the form of medication This sensitivity is an acquired allergy and develops either after the patient has taken the intramuscular injections at regular intervals without interruption for a considerable period of time, or when the injections have been resumed after they have been discontinued for an interval

The symptoms vary in intensity from those considered to be merely a minor annoyance to occasional severe reactions characterized by loss of consciousness and incontinence They usually appear a few minutes following an injection of liver extract and generally can be relieved or prevented by the subcutaneous administration of 0 5 cc of 1-1000 solution of epinephrine hydrochloride The common symptoms are flushing of the face palpitation and tachycardia itching of the skin urticaria stuffiness of the nasal passages and occasionally outspoken asthmatic attacks or loss of consciousness with incontinence of urine Usually when the symptoms have once appeared, it becomes necessary to change the therapy or desensitize the patient as the symptoms usually become progressively worse

The most comprehensive review of this subject is that by Kaufman Farmer and Reich (*308*) They state that since 1931 there have been 35 articles dealing with this subject in which a total of 50 patients are reported as having experienced reactions from liver extract by injection In addition they record 11 additional cases four of which were seen personally by them and seven whose detailed histories were provided by other physicians While reactions to various types of antipernicious anemia medication are not common nevertheless they are observed in every large hematological clinic and are likely to occur in the experience of all physicians who give liver extract intramuscularly as well as other types of treatment There have been few reports of allergic reactions from the oral ingestion of liver either raw or cooked or liver extract as reactions most commonly occur when the medication is given intramuscularly It may follow the use of almost every type of liver extract including the European preparations It is also known that when patients experience a reaction from one brand they are likely to have the same untoward effect from other preparations

To a certain extent the amount of extract injected is of importance but this is not always true It has been reported that a reaction has

acid given orally and a severe anaphylactic reaction later following the intravenous administration of folic acid The patient gave a history of sensitivity to many common drugs The authors consider sensitivity to folic acid as a rare condition since the drug has been employed many times in the last few years prior to their publication without a report of a similar reaction

Untoward Reactions to Vitamin B_1 —It is rare to observe local or general reaction following the parenteral injection of vitamin B_1 but occasionally both types have occurred One patient reported by Arkless (*311*) who received several injections of vitamin B_1 into the deltoid muscles developed a pronounced swelling after an injection which persisted several days later the same result occurred in the other arm Nodules persisted at the sites of these injections for several months The dose causing the reactions was 7 5 micrograms of vitamin B_1 concentrate

Sensitivity to vitamin B_1 concentrate with a general reaction is *reported by Young Ulrich and Fouts (312) Their patient was extremely* sensitive to liver extract and *reacted to vitamin B_{12} concentrate but showed no evidence of sensitivity to crystalline vitamin B_{12}* Within five to 10 minutes after the patient received 5 micrograms of vitamin B_{12} concentrate prepared from streptomycin broth peripheral circulatory collapse developed the blood pressure fell to 40 systolic and zero diastolic the pulse was rapid and weak and perspiration was profuse Recovery occurred in about three hours following the infusion of normal saline solution injections of ephedrine and antihistaminic drugs orally Subsequently the antipernicious anemia therapy was changed from vitamin B_1 concentrate to the crystalline form and the patient showed no evidence of sensitivity

Possible Causes for Failure of Antipernicious Anemia Medication — When a patient who is thought to have pernicious anemia fails to respond properly to the therapy employed what may be the explanation? The following possibilities should be kept in mind

1 The patient may not be taking the medication as directed or the preparation employed may be of low potency These explanations are unlikely at present Almost all antipernicious medications at present are of acceptable potency and if it is administered intramuscularly by a physician it is certain that the patient is receiving the proper medication

2 The diagnosis of pernicious anemia may be incorrect The patient may have subleukemic leukemia myxedema nephritis or some other type of disease with an associated anemia which resembles pernicious anemia superficially Such types of anemia do not respond to antipernicious anemia medication

3 It is recognized that patients with pernicious anemia who have any type of active infection or elderly patients with advanced arteriosclerosis

reasonable to assume therefore that the sensitivity is to some substance in liver, irrespective of its biological source

Treatment of Allergic Reactions to Liver Extract—The immediate symptomatic treatment of allergic reactions to liver extract consists in the injection of epinephrine hydrochloride 1–1000 solution in a dosage of 0 3 to 0 5 cc subcutaneously If there is a local reaction it should be treated with calamine lotion containing a small amount of phenol

In my opinion the most satisfactory method to follow in a patient who becomes *sensitized to the intramuscular injections of liver extract* is to change the therapy to the intramuscular injections of vitamin B_{12} This can be given without reactions to such patients *(291)* An alternative plan but a less satisfactory one is to substitute some type of oral medications such as Ventriculin in doses of 20 to 40 grams daily oral liver extract *in a dose of 12 75 (three level teaspoonfuls) daily, or prob*ably superior to the previously mentioned oral preparations Extralin a stomach liver preparation in a dosage of four pulvules (2 grams) daily

Desensitization by means of gradually increasing doses of liver extract can be accomplished It is suggested by Kaufman and his associates *(308) that the initial injection when such a procedure is carried out* should be 0 1 cc of a 1–10 dilution, and that this should be increased 0 2 cc every second or third day for about three weeks until the patient is receiving a full therapeutic dose of a refined liver extract containing 15 units per cc In their opinion it is important to keep this type of patient *desensitized* by *giving the subsequent therapeutic injections* at more frequent intervals than is customary namely at least once a week

When administering liver extract injections to such patients one should have a 1–1000 solution of epinephrine a sterile syringe and tourniquet at hand for emergency use

Sensitivity to liver extract may *disappear spontaneously When this* occurs it may be possible to resume the liver extract injections With the introduction of the highly efficient vitamin B_{12} form of therapy however there is no indication to revert to liver therapy as extended experience is likely to show that vitamin B_{12} will maintain the blood in a *normal condition and that untoward reactions are* unlikely It is reported by Berk and his associates *(288)* that a patient who suffered severe local and systemic reactions to purified liver extracts derived from both pork and beef tolerated vitamin B_{12} injections without untoward symptoms In their opinion this observation suggests that vitamin B_{12} *is not responsible* for sensitivity reactions to liver extracts

Hypersensitivity to Folic Acid—Ordinarily patients who receive folic acid parenterally do not have unpleasant symptoms with the possible exception of transient flushing and tingling sensations in the *face and* extremities A case is reported however by Mitchell Vilter and Vilter *(310)* who developed a maculopapular dermatitis during a course of folic

elsewhere while the routine use of folic acid alone in the treatment of pernicious anemia is not recommended on account of its unfavorable *effect on the neurological manifestations there is no proof to indicate that when used in combination with liver extract or vitamin B₁₂ it exerts* such an effect On the other hand there is some evidence that the addition of oral folic acid to the therapeutic program in some patients with pernicious anemia is beneficial Certainly a trial of such medications when such circumstances prevail is warranted with the patient under observation

Iron —Ordinarily it is not necessary to give iron preparations to patients with *pernicious anemia because in a great majority of instances there is no evidence of deficiency of this metal in the body With the administration* of antipernicious anemia medication the number of red blood cells usually increases rapidly at the rate of approximately 300 000 to 500 000 per cubic millimeter per week Although there is a simultaneous rise in the hemoglobin content of the blood this is relatively less than the red blood cell increase The color index therefore must fall Without additional treatment this will in most instances soon become normal If there should be an undue delay in this and occasionally it does occur then iron in the form of ferrous sulphate 0 3 to 0 6 gram (5 to 10 grains) should be *given orally three times daily* before meals in the form of enteric coated pills

Rest —At least partial bed rest should be advised in the case of patients in whom the red blood cell count is 2 million per cubic millimeter or less but they should be urged to be up in a chair for short intervals as soon as the blood shows material improvement and this should be increased gradually until they are up for a greater portion of the day as soon as their regained strength warrants it

Transfusions —*In patients in whom the red blood cell count is 1 million per cubic millimeter or less it is generally advisable to give at least one* and in some cases several blood transfusions by the slow drip method This is to make certain that the patient will be sustained until the antipernicious anemia medication becomes effective which requires several days

Diet — The diet should be abundant and the patient s increased appetite satisfied to the fullest Care should be taken to see that ample protein is provided in the form of meat eggs and milk to the amount of approximately 1.5 grams per kilo per day This is useful as it provides an adequate amount of the extrinsic factor which adds its share to the stimulus of red blood cell formation and thereby augments the effect of the liver extract

Vitamin Therapy —If the patient partakes of an abundant diet containing a wide variety of food it does not seem necessary in most instances to reinforce the food intake with vitamin products Some

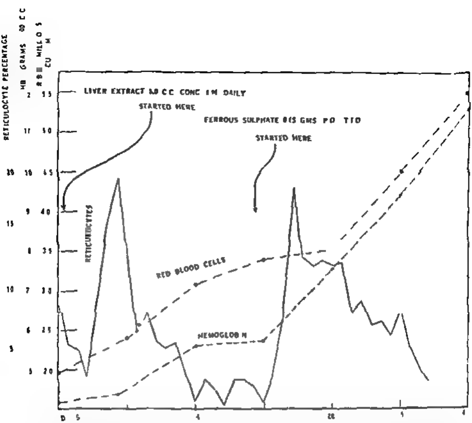

Fig 35 —Showing the effect of liver extract and iron in a patient who had both true pernicious anemia and an associated iron deficiency anemia The latter was due to chronic hemorrhage from the gastro intestinal tract With the administration of 1 cc of liver extract daily there was a reticulocyte rise to 19 per cent and increase in the red blood cell count and to a lesser extent the hemoglobin Despite the daily administration of liver extract the latter remained in the vicinity of 5 5 grams until ferrous sulphate 0 65 gram t i d was given in addition to the liver therapy With this there was a prompt rise in the hemoglobin and red blood cell count and in addition a second rise in the reticulocytes to a peak of 18 per cent Iron therapy is not indicated however in patients with pernicious anemia unless there is an associated iron deficiency anemia which occurs only rarely

changes require a larger dosage of the antipernicious anemia medication The average dose in such patients may be submaximal

4 The diet may be inadequate A deficiency of protein in the diet seems to bear a relation to the ability to form blood at a normal rate Such patients should be encouraged to consume a serving of meat eggs and a pint of milk daily

Such considerations should be investigated in all patients suspected of having pernicious anemia who are not responding as they should to treatment If none of the above suggestions apply to the patient and the diagnosis of pernicious anemia is still entertained then the amount of liver extract or vitamin B_{12} should be doubled and if the blood does not then return to normal the possibility of adding 10 milligrams of folic acid orally per day should be given serious consideration As stated

useful as the patient gains strength. Of benefit are active and passive exercises occupational therapy massage hydrotherapy and local application of heat. The parenteral use of vitamin B_{12} or liver extract in conjunction with coordination exercises have been recommended by Hall, Krusen and Woltman (*315*) in the treatment of subacute combined degeneration of the spinal cord. They re-emphasize that the changes associated with this condition are reversible if intensive treatment is instituted early in the course of the disease before the axis cylinders are destroyed.

Care of the Bladder.—Often of immediate importance when a patient is first seen is an inability of the patient to void urine due to neural changes which involve the control of the bladder. It is advisable in many cases to introduce an inlying catheter although the Credé method of manual emptying may be given a trial. If difficulty in voiding has been experienced for some time usually there is stasis of urine in the bladder and an associated urinary infection. This may be treated by the introduction of an inlying catheter and by bladder irrigations of 0.25 per cent acetic acid employed every two to four hours. Either sulfathiazole or sulfadiazine should be used in doses of 0.5 gram four times daily with due caution in regard to their untoward effects as the most efficient agents in the control of infection. If these drugs fail, then penicillin or possibly streptomycin should be used.

Prognosis and Course of the Disease.—The prognosis in a given patient with pernicious anemia has varied greatly since the disease was first recognized depending on the period in which the results are considered. From the initial descriptions of Addison (1849) and Biermer (1872) until 1926 life expectancy averaged between two and one half to three and one half years with a few notable exceptions due to unusually prolonged spontaneous remissions. With the introduction of liver therapy in 1926 by Minot and Murphy however the outlook completely changed. It should be said however that for approximately the first decade of liver therapy the treatment was often applied in the most inefficient manner. In this period, beginning in 1926 life was prolonged effectively in many patients but it was not generally appreciated that the red blood cell count must be maintained at a high level of normal in order to prevent complicating and severe changes in the nervous system. Death from anemia during this interval was rare. About one half of the patients died of coincidental diseases mainly cancer and cardiovascular disorders whereas the other half succumbed to degenerative changes in the nervous system culminating in a spastic ataxic paraplegia with loss of control of the sphincters of the bladder and the rectum.

Beginning in about 1936 and continuing to the present time the superior results of treatment are shown by the observations of Mosbech and Videbaek (*264*) which are based on a study of 301 patients with

claim, however especially when advanced cord lesions are present that vitamin therapy makes improvement more certain and the results more complete There can be no harm in the oral administration of powdered yeast in doses of 15 to 20 grams daily which should be ample to satisfy all possible vitamin B requirements

During World War II, in England *(313)* where the supply of fresh fruits and vegetables had been curtailed during the winter months on account of war conditions it has been reported that patients with this disease did not respond promptly to antianemia medication because of a vitamin C deficiency I have not observed evidences of this in the United States but in some instances a very low ascorbic acid content of the blood has been noted in my patients This possibly should be kept in mind if the proper anticipated response does not follow liver therapy and ascorbic acid should be given in doses of 50 milligrams three times daily if indicated

Dilute Hydrochloric Acid —It has not been my custom in recent years to prescribe dilute hydrochloric acid routinely in these patients, for to me there is no convincing evidence that it is useful or necessary for the control of the gastrointestinal symptoms or that it exerts a beneficial effect on any other aspects of the disease such as those referable to the nervous system In the first place it is not possible to supply the amount of hydrochloric acid which is normally present in gastric secretions For example it has been shown by Koehler and Windsor *(314)* that the amount of hydrochloric acid secreted by the stomach following an average meal must be in excess of 104 cc normal 35 cc U S P or 3 8 grams in order to bring the pH of the gastric secretions to the normal post meal physiologic level which is from 1 6 to 1 8 They observed that even the large dose of dilute hydrochloric acid of 5 cc recommended by Hurst and Shay and others will bring the pH down to only 4 3 Second although patients with pernicious anemia have probably had an achlorhydria since birth they have been symptomless for a greater part of that time as are almost all of the 5 per cent of the population at large who likewise have an absence of free hydrochloric acid from the gastric secretions Finally in almost all cases the gastrointestinal symptoms disappear following the effective administration of antipernicious anemia therapy In the small per cent in which this does not occur the possibility must be considered that they are due to changes in the nervous system or a complicating cholecystitis or cholelithiasis or possibly cancer of the stomach Regardless of what the cause may be of the residual gastrointestinal complaints hydrochloric acid therapy may be tried for it can certainly do no harm to administer the dilute acid in doses of 1 teaspoonful in a glass of water to be sipped with the meals

Physiotherapy —No attempt should be made to give physiotherapy to patients during the period of severe relapse but such procedures are

follows "The treatment of pernicious anemia is discouraging No patient with true pernicious anemia has ever been cured However successful any therapeutic procedure may have been at first there comes a time when the patient does not react to any treatment He gradually grows worse and death ensues Furthermore no treatment has so far been suggested which can be shown to prolong life

A spontaneous remission is defined by Bloomfield (214) as a situation in pernicious anemia in which there is an improvement in symptoms with a significant rise in the blood count (of at least one million red blood cells per cubic millimeter and/or 20 per cent hemoglobin) This must occur without the introduction of liver or other known antianemic substances He regards it as a term of convenience and a non committal one as to the exact explanation of the phenomenon under discussion In this experience the speed with which the red blood count might rise was remarkable in some instances gains of 1 to 2 million per cubic millimeter within two to eight weeks were not uncommon In the most striking case the count stood between 3 and 4 million per cubic millimeter within a month and the patient felt perfectly well In a series of cases reported by Bloomfield a hematologic remission as he defined it with marked general and systemic improvement occurred eight times in 28 patients who received expectant treatment This gave a percentage of 28 5 The number of days the patient spent in the hospital until the highest count was reached averaged 43 it is clear therefore that a remission will not often be seen if the period of observation is very brief He notes also that remissions are observed more frequently in the early years of the disease and that in all essential features the spontaneous remission resembles that induced by liver therapy This includes the typical reticulocyte response which is well illustrated in the cases reported by Vogel and McCurdy (316)

The conclusions by Bloomfield in regard to spontaneous remissions are as follows He considers that they are not mediated by the introduction of specific antianemic substances This statement is based on the following observations

1 Remissions have been observed in patients who ate no meat liver or other recognized antianemic substances

2 Spontaneous remissions often occur after so long a control period on a certain regime that any effect of diet or other external circumstances seem ruled out

3 Patients maintained on exactly the same regime under which spontaneous remissions took place later suffer relapses This proves that the diet contained no specific antianemic substances

4 Remissions may occur in patients with semicoma unable to take food at all

5 Spontaneous remissions have been observed in patients in the hospital under special control to exclude ingestion of effective material

pernicious anemia who received effective and continuous treatment The follow up period averaged 10 5 years their study being concluded in 1949 On the basis of the population of Copenhagen during 1935–39 it would be expected, when 301 persons of the same age and sex distribution were considered that 89 females and 28 males or a total of 117 persons would die Actually among the patients with pernicious anemia 83 females and 32 males with pernicious anemia, total of 115 did succumb They conclude, therefore as the statistics clearly indicate that female patients with pernicious anemia have the same outlook for survival as normal females in the population at large but there is a slightly but not significantly higher mortality among males

It may be said at present therefore that if a patient develops pernicious anemia and is treated persistently with the most effective present day methods the chances of surviving for a normal span of life are excellent and the possibility of dying of pernicious anemia is almost nil Such a patient will succumb to the conditions which ordinarily cause death in the group of middle aged persons or older with the exception that a significantly larger number of patients with pernicious anemia will die of cancer of the stomach

Spontaneous Remissions—A remarkable phase of the disease the observation of which is denied the younger physician of today on account of the present day effective treatment is the spontaneous remission which was an expected event in almost every patient in which the natural course was pursued It may be described as follows after the patient had suffered from the condition for a variable period of time and often at a time when the anemia was very pronounced rather sudden and dramatic improvement would occur In most instances the red blood cell count increased to 3 5 millions per cubic millimeter or higher often a great majority of the symptoms disappeared and the patient returned to his regular duties after it had been thought by his family and friends and frequently his physician that death had been imminent Such a remission usually persisted for three to six months at the end of which time the red blood cell count again gradually fell and all of the severe symptoms of an anemia reappeared and invariably death eventually ensued Practically all patients had at least one spontaneous remission and some as many as five or six As it was never possible to foretell when such improvement would occur and as many varied types of remedies were administered it is easy to understand that the medication which was prescribed just prior to a spontaneous remission should falsely be given the credit for the betterment of the patient As a result of the illogical application of this sequence of events method of proof many spurious therapeutic claims were made All eventually were disproven as indicated by the hopeless but nevertheless the accurate contemporary appraisal of treatment given by Evans (*111*) as

follows The treatment of pernicious anemia is discouraging No patient with true pernicious anemia has ever been cured However successful any therapeutic procedure may have been at first there comes a time when the patient does not react to any treatment He gradually grows worse and death ensues Furthermore no treatment has so far been suggested which can be shown to prolong life"

A spontaneous remission is defined by Bloomfield (214) as a situation in pernicious anemia in which there is an improvement in symptoms with a significant rise in the blood count (of at least one million red blood cells per cubic millimeter and/or 20 per cent hemoglobin) This must occur without the introduction of liver or other known antianemic substances He regards it as a term of convenience and a non committal one as to the exact explanation of the phenomenon under discussion In this experience the speed with which the red blood count might rise was remarkable in some instances gains of 1 to 2 million per cubic millimeter within two to eight weeks were not uncommon In the most striking cases the count stood between 3 and 4 million per cubic millimeter within a month and the patient felt perfectly well In a series of cases reported by Bloomfield a hematologic remission as he defined it with marked general and systemic improvement occurred eight times in 28 patients who received expectant treatment This gave a percentage of 28 5 The number of days the patient spent in the hospital until the highest count was reached averaged 43 it is clear therefore that a remission will not often be seen if the period of observation is very brief He notes also that remissions are observed more frequently in the early years of the disease and that in all essential features the spontaneous remission resembles that induced by liver therapy This includes the typical reticulocyte response which is well illustrated in the cases reported by Vogel and McCurdy (316)

The conclusions by Bloomfield in regard to spontaneous remissions are as follows He considers that they are not mediated by the introduction of specific antianemic substances This statement is based on the following observations

1 Remissions have been observed in patients who ate no meat liver or other recognized antianemic substances

2 Spontaneous remissions often occur after so long a control period on a certain regime that any effect of diet or other external circumstances seem ruled out

3 Patients maintained on exactly the same regime under which spontaneous remissions took place later suffer relapses This proves that the diet contained no specific antianemic substances

4 Remissions may occur in patients with semicoma unable to take food at all

5 Spontaneous remissions have been observed in patients in the hospital under special control to exclude ingestion of effective material

Such a patient was reported by Barnett (*317*) who developed a reticulocytosis of 10 per cent just as some test material was about to be given in a case in point

6 Evidence that the pernicious anemia patient may from time to time manufacture adequate amounts of intrinsic factor is inadequate

It is emphasized by Bloomfield (*214*) that the spontaneous remission is an essential feature of the natural history of pernicious anemia and hence any theory of the nature of the disease must take this phenomenon into account He does not believe that this is readily achieved by the currently prevailing view that pernicious anemia is a deficiency disease

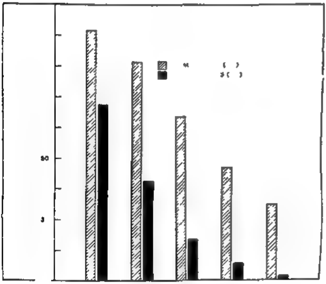

Fig 36—Showing the length of life after the onset of pernicious anemia in patients who have received the modern treatment for the disease (Simpson Memorial Institute Series) as compared with patients who were observed before liver therapy was introduced (Cabot Series) The effect of the modern treatment is apparent for example at the end of 3 years 63 per cent of the treated group are living whereas only 24 per cent of those who did not receive this form of therapy survived The effect of the modern treatment is probably even more striking in recent years now that the more effective form of intramuscular liver treatment is employed almost exclusively

caused by the lack of ingestion formation absorption or storage of a substance which is needed for maturation of the red blood cells If a relapse is due to a lack of this substance it is difficult for him to conceive how it is suddenly provided at the time of remission He does not accept the proof submitted by Isaacs and Goldhamer (*318*) that in patients with pernicious anemia there is a decreased secretion of the intrinsic factor although the evidence appeared to me to be clear and the deductions logical From the evidence suggested by spontaneous remissions in the course of the disease and the other data Bloomfield (*214*) believes support is provided for the view that a toxic hemolytic process is responsible for the anemia of pernicious anemia as well as the constitutional symptoms This is opposed to the present day opinion which is

receiving the widest support namely that pernicious anemia is a deficiency disease and that remission is brought about by supplying a lacking factor which is necessary for the maturation of the red blood cells

Important Factors in Formulating a Prognosis—In formulating the prognosis in the case of any given patient with the disease at present there are three important aspects of the situation which should be given special attention They are (1) the condition of the nervous system (2) the ability and willingness of the patient to cooperate and (3) the status of the patient's general physical condition with reference to the presence or absence of other diseases which are commonly present at middle age or older

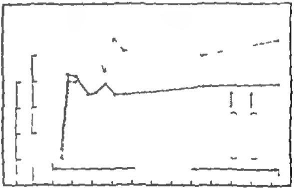

Fig 37—Shows the effect of liver treatment in a patient over an interval of 11 years I have recently had an opportunity to study the patient in 1945 which makes an observation period of 18 years He was found to be in excellent health with a normal red blood cell count and hemoglobin There are no important changes in the nervous system and the patient's complaints referable to his heart are minimal He is now [illegible] years old and has been treated with cooked liver for 18 years with excellent results He has consistently refused to substitute any other form of treatment for the ingestion of whole liver by mouth In the past three or four years he has eaten about one quarter of a pound of cooked liver three or four times a week He continues to work regularly as a watchman in a nearby automobile factory

The Effect of Modern Treatment on Prognosis—Very shortly after the liver treatment of pernicious anemia was introduced it became apparent (319) that the anemia could be controlled with comparative ease but that the main therapeutic problem was the management of the neurological manifestations as they responded much less dramatically and satisfactorily to this form of therapy Some contended that treatment of the neural lesions was of no avail, and it was illogical to expect good results because the changes in the nervous system were due to an actual destruction of the axis-cylinders Hence they were considered to be reversible only when the proper treatment is administered in the early stages

It was observed among the first patients treated that the neurological symptoms and signs might advance during treatment *but it is now known that this occurs only in those who are treated inadequately* During the early days of the liver therapy we were too content to bring the level of

TABLE XXI

RELATION OF ADEQUATE TREATMENT TO CHANGES IN THE NERVOUS SYSTEM IN PATIENTS WITH PERNICIOUS ANEMIA

	Blood Normal Continuously (Per Cent)	*Regular But Inadequate Treatment (Per Cent)*
Improved	87 0	28 6
Unchanged	12 2	42 9
Progressed	0 8	28 5

TABLE XXI —The above table indicates clearly that the neurological manifestations are likely to progress with inadequate treatment and improve or at least remain unchanged when a sufficient amount of therapy is given to maintain the blood at a normal level continuously *The facts illustrate convincingly that a sufficient amount of liver extract or vitamin* B_{12} should be given perferably intramuscularly to maintain the blood at a high level of normal if the neurological changes are to be controlled

the red blood cell count to the vicinity of 3 8 million to 4 0 million per cubic millimeter rather than to 4 5 to 5 0 per cubic millimeter because at the lower level most symptoms of the anemia usually are in abeyance *It is true however that the neurological changes under these circum*stances may advance It is gratifying to know that subsequent observations have shown they do not progress when the red blood cell count is

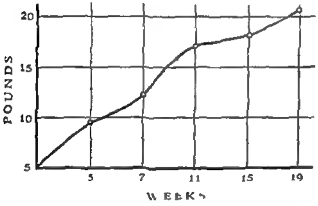

Fig 38 —This figure shows the striking gain in body weight which follows anti pernicious anemia therapy The same effect on the body weight follows the use of either ventriculin or liver extract The average *increase is uniformly* upward with a total gain for the entire group of 50 patients averaging slightly over 20 pounds in 19 weeks (Sturgis and Isaacs courtesy *Annals of Internal Medicine*)

maintained at a high level of normal and may even show remarkable evidence of improvement In my experience I can state that rarely have the neurological manifestations progressed unfavorably when the *blood has been kept constantly at a normal level I have* commonly seen them become more pronounced when a slight though definite anemia has persisted either as a result of inadequate therapy or because it has not been possible to maintain the blood at normal on account of a complicating infection Table XXI shows the effect of adequate treatment

In a study of the relation of therapy to changes in the nervous system in 70 patients with pernicious anemia who were observed at the Simpson

Memorial Institute for a minimum period of 10 years Bethell and Sturgis (320) concluded as follows first, in 36 patients who received treatment regularly and were maintained consistently in complete hematological remission there was no evidence of development or progression of the neural lesions In a second group of 15 patients who did not adhere strictly to an optimal therapeutic regimen the blood was frequently abnormal although definite relapses did not occur Adverse changes in the nervous system did occur but they were transient and reversible when adequate therapy was resumed In a third group of 19 patients there were definite clinical and hematological relapses which were associated with the development or progression of neurological manifestations It is of interest to note however that serious progression and severe permanent injury to the spinal cord was rarely observed *This eventual favorable course of the neural changes in many of these patients is probably attributable to the short duration of the relapses and the relative mild degree of nervous system involvement when the diagnosis was made*

The situation concerning the prognosis as relating to the spinal cord changes differs now from what it did in the first 10 years of liver therapy In the earlier period three matters then contributed to the ominous prognostic significance of the neural manifestations first the therapeutic agents were less effective and second relapses usually progressed to a further state than at present and third it was not then appreciated that the red blood cell count must be kept constantly at a high level of normal if adverse neurological manifestations are to be averted

It is of interest to note that in my own series of 150 fatal cases of pernicious anemia (321) it is recorded that in patients with pernicious anemia observed between 1927 and 1939 51 fatalities were due to pernicious anemia but only seven died of the anemia and *44 of spinal cord changes* and 49 died of coincidentally associated disease mainly heart disease cancer cerebrovascular accidents and pneumonia. Hence about 30 per cent of the deaths in this early series was attributable to involvement of the nervous system About 47 per cent died of unknown causes as death occurred outside of the hospital

It is now recognized that the outlook for improvement does not depend so much on the extent of the involvement as it does on the duration of the neurological lesions In general it may be said that the more recent the involvement of the nervous system the better the outlook for improvement as the most favorable responses are obtained when they have been present less than a year One patient who has been under my observation for a period of over 20 years had a paralysis so extensive that bed rest was imperative as he could not stand unassisted He made a complete recovery and can now mow his own lawn and walk several miles without tiring I attribute his remarkable recovery to the fact that

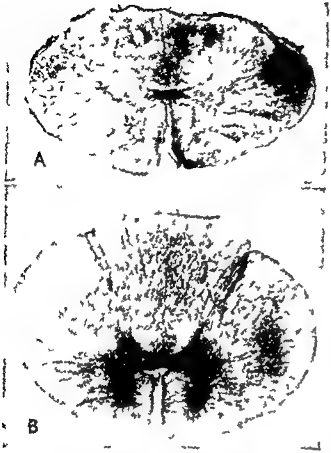

Fig 39 —A shows a transverse section of a low thoracic segment of the spinal cord of a patient with pernicious anemia who had been given liver therapy There is severe demyelinization involving the posterior tracts of the white matter and of the direct and crossed pyramidal tracts The spinal cord is small and shows anterior posterior flattening (Weigert stain) B shows a transverse section of a low thoracic segment of the spinal cord from a patient with pernicious anemia who had a severe subacute combined degeneration but received practically no liver treatment The normal contour of the cord contrasts strikingly from that shown in A which was cut from approximately the same anatomical level Magnification × 14 (Hyland and Farquharson courtesy *Archives of Neurology and Psychiatry*)

his symptoms had been present for only about six weeks and because a high dosage of intramuscular liver extract was given which maintained his red blood cell count constantly in the vicinity of 5 million per cubic millimeter

No improvement was observed by Hyland and Farquharson (322) in their patients if the neurologic disturbances had been present for a period of four years or more I am in accord with this statement but believe that it is more accurate to state that symptoms, which have been present as long as two years are very unlikely to respond favorably Furthermore the maximum improvement that one is likely to obtain with optimum therapy is usually apparent after a period of one year and usually much before that time I am in further agreement with Hyland and Farquharson (322) that the manifestations which show the best response to therapy are paraesthesia impaired joint sense and gait, diminution of superficial sensation and disturbance of sphincter control There is frequently a gratifying tendency to recover from psychic disturbances Those signs which are more refractory to therapy are the impairment of vibratory sense the Babinski reflex and absence or decrease of the Achilles reflex

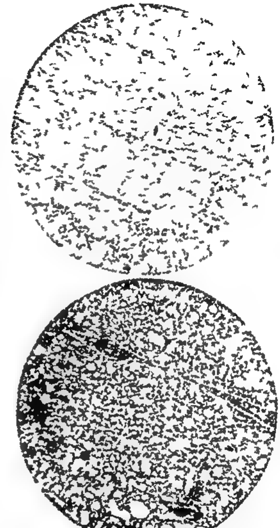

Fig 40 —Shows a transverse section from a degenerate area of the posterior columns taken from the same level as shown in Figure 39A (p 338) Note the condensation of tissue in the degenerated white matter with no evidence of activity of the disease Hematoxylin and eosin stain × 187 B shows a transverse section from a degenerate area of the posterior columns of the same thoracic segment shown in Figure 39B (p 000) Note the vacuolation indicating an active degenerative process Compare with A Hematoxylin and eosin stain × 187 (Hyland and Farquharson courtesy *Archives of Neurology and Psychiatry*)

The second aspect of the neurological lesions which is important from the standpoint of prognosis is their extent It is possible to divide all neurological manifestations into four groups from this standpoint the first group having the most favorable prognosis and the fourth the most ominous The four groups are as follows 1 patients in whom the sole complaint referable to the nervous system is numbness and tingling of the hands and feet which probably indicates that only the periperal nerves are involved 2 patients with evidences only of involvement of the peripheral nerves and posterior columns as shown by ataxia and impairment of the sense of motion and position and the vibratory sense 3 those with the classical features of subacute combined degeneration of the spinal cord and 4 those with evidence of the changes in group

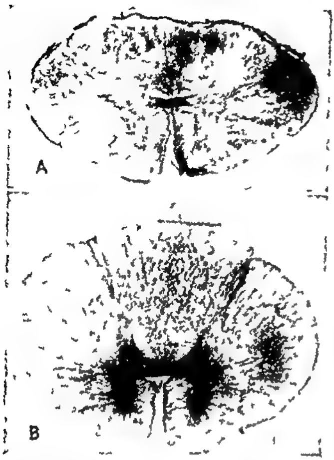

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TABLE XXII

CAUSE OF DEATH OF 147 PATIENTS WITH PERNICIOUS ANEMIA

		Patients	
		Number	Per Cent
1 Unknown		47	31 97
2 Pernicious Anemia			
Anemia	7		
Spinal Cord Changes	44	51	34 70
3 Other Diseases		49	33 33
		147	100 00

TABLE XXII —Showing the cause of death in 147 patients with pernicious anemia in the interval after the introduction of liver therapy into clinical medicine Approximately one third of the patients died of unknown causes one third of pernicious anemia and one third of unrelated diseases It is probably correct to assume that approximately one half of the deaths from unknown causes were due to pernicious anemia and the remaining one half to unrelated diseases If this is true it can be said that a patient with pernicious anemia has an equal chance of dying of this condition or some unrelated disease With improved methods (parenteral) of treatment even a smaller group die of pernicious anemia at present. (Sturgis Courtesy *Transactions Association of American Physicians*)

an adequate dosage of liver extract but if this form of treatment is given in amounts too small to maintain the blood in a normal condition then the lesions of the nervous system will progress and the prognosis becomes more grave Our own experience furnishes ample proof of these statements For example 85 per cent of our patients showed improvement in their neurological manifestations when treated efficiently with a refined concentrated liver extract intramuscularly and in only 2 per cent was there an advance of the symptoms On the other hand only 28 6 per cent of the patients in whom the treatment had been inadequate exhibited improvement and 28 5 per cent showed an unfavorable progression

The Relation of Coincidentally Associated Diseases to the Prognosis — In a survey made of our fatal cases (321) some years ago it was found that *about* one half died of complications incident to the involvement of the nervous system and the other half of coincidentally associated diseases The latter cause of death is to be expected because if patients with pernicious anemia are saved by the modern treatment it is logical to anticipate that they will succumb to the common causes of death in persons of middle age or older These are most frequently heart disease hypertension cancer pneumonia and cerebrovascular accidents

In a more recent study by Mosbech and Videbaek (261) of the cause of death in 115 patients with pernicious anemia there is a notable difference from the results reported from the Simpson Memorial Institute (321) because pernicious anemia was the cause of death in only three patients and *not a single patient died of neurological involvement* Two of the patients who died were markedly debilitated senile females with

3 but who in addition have a loss of control of the sphincters of the bladder and sometimes the rectum and often with an associated infected urinary tract It is in the last *group that the poorest results so often* follow even the most efficient treatment On the other hand, if the advanced neurological changes are of recent development surprising improvement is sometimes obtained In many instances however the bladder becomes infected and eventually the entire urinary tract With this infection any form of antipernicious anemia therapy becomes less

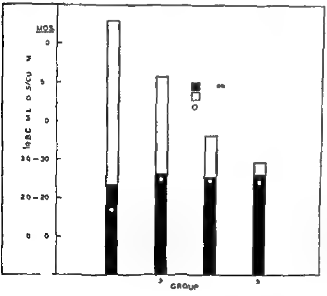

Fig 41 —Figure showing that the period of survival of patients with pernicious anemia is directly proportional to the extent of the neurological involvement In all four of the groups the symptoms of pernicious anemia had been present for 23 to 26 months when the patients were first observed at the Simpson Memorial Institute The average red blood cell count was approximately the same in all four groups as shown by the white dot in the black background The black columns show the duration of symptoms before coming under our observation and the superimposed white columns the duration of life after we had instituted treatment It is apparent that group 2 with minor neurological complaints survived a much longer period than group 5 who had advanced neurological manifestations complicated with a spinal cord bladder

effective and it is not always possible despite intensive therapy to maintain the peripheral blood at a normal level In all patients with any type of infection the usual dosage should be doubled or trebled but even this augmented dosage is not always productive of good results In recent years with the introduction of sulfonamide and antibiotic preparations for treating urinary infections the prognosis in patients with such a complication has been greatly improved

Undoubtedly at present it is generally agreed that the most important single factor in evaluating the prognosis is the degree of nervous system involvement and how it responds to therapy It has been repeatedly impressed upon those responsible for the treating of large numbers of patients with the disease that these manifestations can be controlled by

unless treatment is continued and furthermore all patients regardless of their apparent excellent state of health should consult their physician at least every three months for a complete blood study

If antipernicious anemia medication is discontinued some patients will relapse within a period of about six weeks Others however may continue to remain in good condition for as long as nine months and sometimes as long as two years or more I have seen one patient with pernicious anemia who had remained in good condition for four years despite the discontinuance of all therapy It is difficult to understand why there should be such a long continued period of good health in the absence of therapy unless one assumes that some patients for unknown reasons during the course of treatment enter a stage similar to that which exists during a spontaneous remission This fact illustrates why the maintenance dose method of assaying preparations is not entirely ideal and may lead to false conclusions

A careful study of relapses following the interruption of therapy has been made by Jones Tillman and Darby (300) They discontinued all liver extract therapy in 12 patients with pernicious anemia who had up to that time been adequately treated and kept the patients under close observation Six of the 12 patients relapsed within a period of eight to 18 months but the remaining six patients failed to show hematological relapse over a period of 26 to 29 months following the withdrawal of the liver extract None of the entire group of 12 patients whether in relapse or not developed complaints of any sort and were followed with examinations for evidence of neurological disease glossitis and diarrhea Furthermore there were no important changes in body weight No cause was apparent to these observers for the differences in the time required for relapse to occur in the 12 patients observed In their opinion there was no correlation between the time of relapse and the amount of liver extract therapy which had been administered in the year prior to withdrawal Despite these observations it appears logical to me that in treating patients with pernicious anemia it is advisable to err on the side of administering an excessive rather than a suboptimal amount of antipernicious anemia medication This is because there are reasons to believe that the material can be stored in the body and despite suggestive evidence to the contrary it may be at least one important contributing factor to delaying relapse if antipernicious anemia medication is discontinued

A study of relapses in 54 patients with pernicious anemia has been made by Schwartz and Legere (248) with somewhat different results than those reported above These patients were all from an economic level below average and had been treated at the Cook County Hospital in Chicago The patients disappeared from observation at intervals ranging from immediately following their discharge from the hospital until

Table XXIII

COINCIDENTAL DISEASES AS CAUSES OF DEATH IN 147 PERNICIOUS ANEMIA PATIENTS

	Number of Patients
Heart Disease	11
Cancer	11
Hemiplegia	7
Pneumonia	5
Nephritis	3
Accidents	2
Pulmonary Embolism	2
Following Surgical Operations	2
Hypertension	1
Cirrhosis of the Liver	1
Cyst of the Brain	1
Septicemia	1
Acute Appendicitis	1
Pulmonary Tuberculosis	1
	49

Table XXIII—The above table shows the main causes of death due to unrelated diseases in 147 fatal cases of pernicious anemia. Approximately one third of the patients died of conditions which had no relation to pernicious anemia and are diseases which are the common causes of death in persons of this age group

a severe anemia in whom adequate therapy failed to avert their death and the third patient refused treatment and died at home of a severe anemia two weeks following discharge from the hospital The causes of death in the group of 115 fatal cases studied by these observers (*264*) were as follows heart disease 28 per cent cerebral disorders apart from tumors 21 per cent cancer 18 per cent pulmonary diseases apart from cancer 17 per cent urinary disorders 6 per cent gastro intestinal disorders 5 per cent *pernicious anemia 3 per cent* miscellaneous 2 per cent It is of interest to note that 21 patients died of carcinoma which figure corresponds to the number of anticipated cancer deaths in this area Fourteen died of cancer of the stomach however whereas the anticipated death rate from this disorder indicated that only five in the population at large would succumb to cancer of this viscus

Cooperation of the Patient in Relation to Prognosis—The final consideration upon which a prognosis is to be based is the ability of the patient to cooperate *Failure to follow the physician's advice is not always* because the patient is unable to obtain the proper treatment due to financial reasons but because many patients will not continue to take medication *at a time when they are free from symptoms* Furthermore if a person omits a few doses of antipernicious anemia medication the ill effects are not at once apparent and it is quite easy to understand why a patient will conclude that continued therapy is unnecessary *All patients therefore should be warned that a relapse will inevitably occur,*

Experience with the modern treatment during the past 25 years has led me to the following conclusions concerning the results which may be expected in regard to the prognosis

1 Provided appropriate treatment is persistently administered the chances of any given patient with pernicious anemia surviving in good health for a normal span of life are excellent

2 A patient with pernicious anemia is unlikely to die of anemia or subacute combined degeneration of the spinal cord but will probably succumb to one of the leading causes of death in persons over 50 years of age namely heart disease cancer apoplexy pneumonia or nephritis

3 Although deaths from cancer are no greater in patients with pernicious anemia than in a comparable group of patients in the population at large the number of those who die of cancer of the stomach is greater

4 In patients who have not been treated properly which is usually due to their failure to cooperate death will most likely be due either to coincidentally associated diseases or to subacute combined degeneration of the spinal cord although a few may die of the anemia

MACROCYTIC ANEMIA OTHER THAN PERNICIOUS ANEMIA DUE TO VARIOUS CAUSES

Relation of a Decrease in the Extrinsic Factor to Macrocytic Anemia — Experience has shown conclusively that a deficient diet if followed over a sufficient period of time will result in a macrocytic anemia with a megaloblastic bone marrow The anemias designated as nutritional macrocytic anemia tropical anemia and exogenous pernicious anemia are all apparently associated with a deficient dietary intake It is possible that the macrocytic anemia of liver disease refractory megaloblastic anemia and even pernicious anemia sprue and anemia of pregnancy may also be due in part at least to deficiencies in the diet of either the extrinsic factor which is probably vitamin B_{12} or of folic acid

Groen and Snapper (*323*) reported two patients with features simulating pernicious anemia who had received a deficient diet for a long time Both secreted free hydrochloric acid but the quantity of gastric juice was reduced One responded to autolyzed yeast and the other to liver It was the authors opinion that the macrocytic anemia in these cases was the result of a deficiency of the extrinsic factor Another case is reported by Alsted (*324*) who states that it is very likely that the anemia was due to a deficiency in the food intake The patient a male age 43 years had a red blood cell count of 1 3 million per cubic millimeter a high color index pronounced glossitis the characteristic picture of pernicious anemia in the sternal marrow and a typical distribution curve of the Price Jones measurements Against the diagnosis of pernicious anemia was a normal icterus index and the presence of free hydrochloric acid in the gastric secretions Apparently the nervous system had

45 months later In practically all instances the discontinuance of therapy was voluntary Those who discontinued treatment returned in relapse at intervals varying from two to 38 months About 33 per cent relapsed during the first six months 36 per cent during the next six months 24 per cent during the second year 5 per cent during the third year and about 1 per cent later One patient (*248*) in an observation period of 10½ years had 12 relapses the last one complicated by a fracture resulting in his death

The record given by these observers is representative of the most uncooperative group with which we have to deal in medicine and is not necessarily a reflection on the modern treatment of pernicious anemia It merely shows that in order for treatment to be effective it must be taken regularly in a manner similar to insulin in diabetes or desiccated thyroid in myxedema These observers believe that the factor of relapse is a highly singular phenomenon which is even remarkably inconsistent in the individual patient They believe that the relapse period is intimately connected with quantitative secretion of the intrinsic factor other essential dietary factors and the storage of the antipernicious anemia principle in the liver Furthermore they consider that in addition there is some unknown factor also associated with the tendency to relapse because no correlation is demonstrable between the time of relapse and the average amount of liver necessary for maintenance They suggest that this unknown factor may be associated with that which is responsible for the spontaneous remissions so commonly seen before the days of liver therapy

In 21 instances treatment was discontinued on the patient's own initiative in the group observed by Hardgrove and his associates (*122*) It was noted by them as it has been by others that the time necessary for the manifestations of the disease to appear again is variable in different patients

General Conclusions Concerning the Prognosis —*In general* it may be said that when a patient with pernicious anemia is observed for the first time it is not possible to state exactly the anticipated length of life or what will be the cause of death Experience before 1926 when the modern treatment was introduced sufficed to demonstrate that the natural course of the disease usually terminated fatally within an average time of about two to three years after the appearance of the earliest symptoms Occasionally there would be a period of prolonged remission persisting over eight to 10 years but this was considered to be an exceedingly rare exception In one instance I observed such a remission which had a duration of 10 years and fortunately when relapse did occur the liver treatment had been introduced and the patient survived for an additional period of time Remissions have been reported with a duration as long as 22 years but this is a most unusual occurrence

anemia due to a deficiency of the extrinsic factor and to impaired absorption from the intestinal tract

The following patient whom I observed appears to have had an anemia due to a deficiency of the extrinsic factor and also of iron He was a 24 year old male who entered the hospital with evidences of a pronounced anemia which was borne out by a red blood cell count of 1 7 millions per cubic millimeter and a hemoglobin percentage of 38 per cent (6 0 grams) The white blood cell count was 2700 per cubic millimeter the mean corpuscular volume 135 cubic microns and the mean corpuscular hemoglobin concentration 26 per cent Sternal puncture showed the characteristic findings of a megalocytic anemia with active erythropoiesis and many large megaloblasts some in mitosis "Free" hydrochloric acid was present in the gastric secretions He gave the remarkable dietary history that he had subsisted since childhood on a diet which consisted mainly of coffee and doughnuts with a small amount of milk daily The only explanation which he gave for such an abnormal food intake was that since the age of one year when he had pneumonia "he had been unable to eat regular food" His intake was obviously deficient in animal protein vitamin A thiamin ascorbic acid and niacin An attempt was made to treat him with a high protein intake but this was unsatisfactory as he refused to cooperate As a result his blood cell count fell to an alarming level which necessitated blood transfusions and injections of liver extract 1 cc containing 15 units twice weekly This caused a prompt reticulocyte response and an increase in the red blood cells to 3 5 million per cubic millimeter and a hemoglobin of 73 per cent in about four weeks at which time he was discharged to continue further treatment at home Several months later the red blood cell count reached 5 7 millions per cubic millimeter and the hemoglobin was over 15 6 gram (100 per cent) The liver extract was discontinued for over one year the patient partook of an average dietary intake and his blood remained within normal limits

The role of the extrinsic factor in the causation of a macrocytic anemia cannot be definitely determined at present (1) on account of our incomplete knowledge concerning the extrinsic factor (2) because it is not possible to determine in any given patient the relative importance of folic acid and vitamin B_1 deficiency and (3) the deficiency of the extrinsic factor may be only one contributing cause of the macrocytic anemia which varies in importance at different times

The evidence at present indicates that the heat stable extrinsic factor is soluble in 70 per cent alcohol insoluble in 95 per cent alcohol it is not soluble in ether and passes through an ultra filter At present it is generally considered that vitamin B 12 is the extrinsic factor and that it is closely identified with the liver principle if not identical with it The extrinsic factor is found in lean muscle (beef) liver kidney spleen,

escaped involvement as there was not even the complaint of numbness or tingling of the hands and feet A thorough examination failed to disclose evidence of idiopathic steatorrhea intestinal stricture intestinal parasites pellagra, syphilis, tuberculosis chronic nephritis Hodgkin's disease or any other of the diseases which are occasionally accompanied by a macrocytic anemia No specific mention is made however of the possibility of liver disease or the employment of tests for liver function which are important as it is known that a macrocytic anemia may be associated with pathologic changes in this organ The patient had been on a restricted diet for seven or eight years which was deficient in meat eggs and milk The author regards these articles of diet as the chief sources of the extrinsic factor It is claimed that conclusive evidence of a deficiency of extrinsic factor was obtained when a complete remission, including a reticulocyte response followed treatment with nothing but extrinsic factor and plenty of ordinary food The patient was in good health seven months later without additional treatment when the report was made It is the opinion of Alsted that exogenous pernicious anemia occurs more frequently than is generally believed but that its presence is obscured because both stomach and liver preparations are equally effective in both the exogenous and endogenous form

The studies of Wintrobe (*325*) also lend some support to the claim that an exogenous form of pernicious anemia exists He observed that the administration of 45 grams or more of autolyzed yeast daily will cause a remission in about one third of the patients with pernicious anemia He is of the opinion that the effect may be due to the high concentration of the extrinsic factor in yeast but that one is not justified at present in drawing final conclusions concerning this matter

Other information which may have a bearing on this problem is that furnished by the studies of Bethell and his associates (*326*) which indicates that the macrocytic anemia which is observed in pregnant women of this region responds satisfactorily to the addition of protein to the diet in the form of meat eggs or milk or to the administration of yeast As determined by Goldhamer (*327*) it cannot be concluded definitely from these studies that the anemia is due to a deficiency of the extrinsic factor but this is a possibility Bethell (*328*) is inclined to attribute it to changes in the liver which result from a low protein diet

Studies of the macrocytic anemia in patients who showed or had shown evidences of pellagra all of whom had partaken of a diet deficient in protein are reported by Moore and his associates (*329*) These important observations are discussed under the heading of macrocytic anemia in pellagra (pg 370) In three of the patients it was demonstrated that the intrinsic factor was present in the gastric secretions and in six there was a therapeutic response to the administration of 250 grams of raw beef muscle They conclude that these patients had a macrocytic

pregnant women usually between the ages of 20 and 30 years This condition resembled pernicious anemia in that the blood and bone marrow pictures were identical It differed in certain important features however as follows the age incidence was not the same it occurred more frequently in females hydrochloric acid was usually present in the gastric secretions neurological manifestations were not present glossitis was uncommon response to refined liver extract was irregular but autolyzed yeast crude liver extract and folic acid were effective Furthermore following efficient treatment and the administration of an adequate diet the patient apparently made a full recovery

Although the disease was first described in pregnant women it is also observed in non pregnant women and in males It has been suggested by Napier (332) that the cases now described under this heading may be found to include several distinct varieties From a survey of the literature it seems likely that in almost all patients there is an obvious and striking dietary deficiency especially with reference to proteins and fats The possibility that there may be a deficiency in conjugated folic acid must be given serious consideration It is also clear that commonly the condition as encountered in the natives of India is complicated by pregnancy hookworm infestation syphilis and malaria *In summary* therefore it seems likely that tropical macrocytic anemia may be due primarily to a food deficiency possibly to conjugated folic acid and other still unrecognized dietary factors and that the severity of the anemia may be increased by various other etiological conditions mentioned above

The outstanding symptoms are those of a severe anemia such as weakness ease of fatigue anorexia dyspnea and palpitation and pallor Occasionally there is glossitis and atrophy of the papillae of the tongue The spleen may be enlarged but this is usually due to a complicating malaria

Treatment is with folic acid 10 milligrams daily by mouth and the administration of a full well balanced diet with special reference to protein and vitamins In some patients there may be also an iron deficiency either in association with pregnancy or as the result of bleeding from the uterus or the gastrointestinal tract In such patients the administration of iron orally in the form of ferrous sulphate 0 3 gram t i d after meals is indicated

Macrocytic Anemia in Liver Disease —Anemia in extensive disease of the liver especially cirrhosis is to be anticipated in a great proportion of patients because certain etiologic factors are almost always present For example in cirrhosis *bleeding from esophageal varices* will tend to cause a microcytic hypochromic anemia As the disease is usually observed in patients who consume an abnormal diet either due to alcoholism or personal food idiosyncracies there is a likelihood that the *extrinsic factor may be lacking* and a macrocytic anemia result Likewise vitamins such

pancreas eggs whole grain rice polishings tomatoes and marmite It is present, but in small amount in fish milk cream and bread

In concluding that the extrinsic factor may be the cause of a macrocytic anemia in any given patient ideally it should be demonstrated that (1) the patient has had a diet obviously *deficient in animal protein* (2) that the intrinsic factor is present which is a matter of difficult technic (3) that a liver disturbance is not present as indicated by normal liver function tests (4) that an 80 per cent alcoholic extract of beef muscle which is practically free of protein but is known to contain the extrinsic factor *can produce a reticulocyte rise and an increase in the red blood cell* count when added to the diet (5) that the patient can remain in good health for an indefinite period with no other treatment than a normal diet and (6) that no other condition is present such as intestinal stricture or other abnormalities which might be responsible for a macrocytic anemia

It is appreciated of course that the conditions stipulated above cannot always be fulfilled Admittedly therefore it is most difficult to establish beyond the question of a doubt that a deficiency of the extrinsic factor contributes to the production of a macrocytic anemia or is the sole cause of it Certainly it appears to be a conservative statement to make for the *present that an anemia due to such a cause may exist in some patients* In others it may be an important secondary cause when operating in conjunction with a decrease in the intrinsic factor or with impaired intestinal absorption and possibly with unknown factors

A dietary deficiency in folic acid might also be the cause of a macrocytic anemia *It is possible that this may be at least a contributing* factor if not the sole cause of the macrocytic anemia in pregnancy sprue tropical macrocytic anemia possibly refractory megaloblastic anemia and nutritional anemia Folic acid is present in relatively large amounts in the green leaves of many plants liver kidneys yeast mushrooms and *cereals*

The *treatment of an extrinsic macrocytic anemia* is first place the patient on a liberal diet containing at least one adequate serving of meat eggs and milk daily if this cannot be accomplished on account of the patient s inability to cooperate then folic acid 10 milligrams daily should be given orally finally if the response to folic acid is inadequate then refined liver extract or vitamin B_{12} therapy should be given in addition to folic acid in the same dosage as employed in pernicious anemia

The various types of nutritional anemias are discussed by *Hall (330)* and among other types he considers those due to deficiencies of folic acid and of vitamin B_{12} In his opinion nutritional anemia is seen less frequently as a result of an inadequate intake of food than as a complication of faulty absorption and assimilation from the gastrointestinal tract of hemopoietic factors *normally present in food*

Tropical Macrocytic Anemia —In 1930 Lucy Wills and her associates *(331)* described a type of macrocytic anemia occurring especially in

these three patients and similar ones reported in the literature *are examples of extrinsic factor deficiency macrocytic anemia in persons with cirrhosis of the liver rather than the macrocytic anemia of chronic liver disease*

In a comprehensive study of the diameter of red blood cells in 26 cases of acute hepatitis 32 cases of chronic hepatitis (which included cases of cirrhosis of the liver) and 14 cases of cholecystitis or cholelithiasis (obstructive jaundice) it is stated by Larson (336) that the associated anemia in such patients is characterized by erythrocytes which have an increased diameter while the mean corpuscular volume remains normal In other words the cells are enlarged in diameter but flattened In his opinion the macrocytosis is due to the appearance of a distinct new group of larger red blood cells in the peripheral blood so that the blood cell population becomes heterogenous consisting of a mixture of normal and pathological large cells

An important difference of opinion concerning the blood findings in patients with cirrhosis of the liver is centered about the question as to whether a macrocytic anemia with a true megaloblastic bone is ever present in patients with this disease It is stated by Castle (337) that in cirrhosis of the liver although frequently a macrocytic anemia is present the bone marrow does not exhibit the classical megaloblastosis of pernicious anemia and the anemia rarely responds to therapy with liver extract In his opinion when the patient with cirrhosis responds to liver extract which he believes rarely happens the existence of cirrhosis may be explained as coincidental to pernicious anemia or vice versa On the other hand Movitt (338) supporting the observations of Jerrold and Vilter (335) previously mentioned reports three patients who undoubtedly had cirrhosis of the liver a macrocytic anemia and a megaloblastic bone marrow Moreover in two of the cases there was a response to vitamin B_{12} or liver extract with high protein feeding This treatment caused a reticulocyte response and return of the blood to normal with a reversion of the bone marrow from a megaloblastic to the normoblastic type There can be no question that these patients had cirrhosis of the liver a macrocytic anemia a megaloblastic bone marrow a reticulocyte response following antipernicious anemia medication and a return of the bone marrow to the normoblastic type *But it is unlikely that they had pernicious anemia mainly because all three patients had free hydrochloric acid in the gastric secretions*

It was suggested by Wintrobe and Schumacker (339) in 1933 and later by Wintrobe in 1936 (340) that anemia in cirrhosis results from the inability of the damaged liver to store the antipernicious anemia factor This view was supported by the observations of Goldhamer *et al* (341) who found that a cirrhotic liver may not contain the active principle and that a pernicious anemia like blood picture may develop if such a liver is unable to store the active principle or cannot present

as niacin ascorbic acid and possibly others may be ingested in sub optimal amounts Also it should be taken into account that such patients occasionally may have *true addisonian anemia actually associated* It must be admitted however, that the most frequently encountered anemia associated with this disorder a macrocytic anemia with a normoblastic bone marrow, is due to *obscure etiological factors*

In a series of 132 patients with cirrhosis of the liver reported by Wintrobe (*333*) in *1933*, it was found that no anemia was present in *22 7 per cent* a macrocytic anemia in *32 6* per cent normocytic anemia in 30 3 per cent and a microcytic anemia in 14 4 per cent The latter type he attributed in most instances to chronic blood loss

In a study of 25 patients with cirrhosis of the liver verified by biopsy Berman *et al* (*334*) found that 21 (84 per cent) had an anemia Sixteen of the patients had a macrocytosis three had normocytosis and two had microcytosis Approximately three fourths had a macrocytosis or a macro cytic anemia In 84 per cent the mean corpuscular hemoglobin values were normal or elevated Microcytic hypochromic anemia which oc curred rarely was associated with blood loss from the gastrointestinal tract They concluded that the principal blood findings in their group of 21 patients was a macrocytic or normocytic anemia with normal or elevated mean corpuscular hemoglobin values lymphopenia and throm bopenia in a majority of cases The bone marrow consistently showed ex tension of the red marrow into the shafts of the long bones exhibiting active hematopoiesis The marrow of the sternum was of normal or in creased cellularity with normal or increased erythrocytogenesis and mega karyocytogenesis in most cases They conclude that macronormoblastic *erythropoiesis is seen in patients with macrocytic anemia but megalo blastic erythropoiesis does not result from cirrhosis of the liver* In patients with chronic hemorrhage the blood and bone marrow pictures were those of iron deficiency anemia although other changes as lympho penia and thrombocytopenia had a tendency to persist

The most commonly encountered anemia found by Jerrold and Vilter (335) in 30 cases of proven cirrhosis of the liver was the macrocytic type with a normoblastic bone marrow which usually responded poorly to liver extract Three of their patients however did have a macrocytic anemia associated with a megaloblastic marrow similar to that characteristic of pernicious anemia These patients had eaten a diet for years which had been grossly deficient in B complex vitamins animal proteins and pre sumably in the extrinsic factor The anemia responded either to liver extract or to the addition of ground beef to the diet Evidences of vitamin B deficiencies were present in these patients namely glossitis neuritis and pellagrous dermatitis One of these patients had free hydro chloric acid in the gastric secretions following histamine stimulation the other two had none It is the opinion of Jerrold and Vilter (335) that

(344) who state that removal of the stomach in the human subject is "rarely followed by pernicious anemia

A majority of observers however do not agree with these opinions for it is known that total gastrectomy in humans is sometimes followed by a macrocytic anemia which is identical with pernicious anemia Meyer Schwartz and Weissman (345) summarized the literature to 1941 relating to this association and report that there were 54 cases of pernicious anemia which developed following this operation In the published accounts the following points were stressed the symptoms and typical hematological picture *develop within two to 15 years after the operation* evidence of subacute combined degeneration of the spinal cord often accompanies the anemia gastrointestinal symptoms are almost always observed the response to antipernicious anemia medication is specific and dramatic

The observations of Farris Ransom and Coller (346) suggest that following the removal of the entire stomach at least a considerable period of time may be required before a macrocytic anemia appears These observers report that total gastrectomy was done on 29 patients at the University of Michigan Hospital since 1937 and that 24 of these patients survived the operation By total gastrectomy the authors mean the complete removal of the stomach with a segment of the esophagus and duodenum attached Many of these patients developed an anemia of the microcytic hypochromic type probably due to an iron deficiency at least the anemia responded promptly to the proper doses of that metal Of their 29 patients only four had been under observation for as long as two years when their publication appeared and in none of these had a macrocytic anemia developed

Assuming that no antipernicious anemia medication had been taken then some explanation must be offered to explain why the complete absence of the stomach is not followed in all such patients by the development of a macrocytic anemia It is doubtless true that with a longer period of observation some of them if untreated with liver or stomach preparations will develop a macrocytic anemia But even if this does occur it must be assumed that the body is provided with a sufficient reserve supply of the erythrocyte maturing factor to cause a normal maturation of the erythrocytes in the bone marrow for two years or longer Or must it be concluded that some other portions of the body can assume the functions of the stomach glands in providing the intrinsic factor? It is certainly true that a sufficient number of patients have developed the blood picture of pernicious anemia following total gastrectomy to eliminate the possibility of a coincidental association The explanation of the long latent period following gastrectomy and the apparent failure of some patients to develop this form of anemia following such an operation indicates clearly that our knowledge concerning this matter is still incomplete

it to the body tissues in the proper form for utilization In 1938 however, it was reported by Schiff Rich and Simon (342) that the active principle could be recovered from the livers of patients with cirrhosis and a macrocytic anemia They considered that such an anemia developed on the basis of defective utilization rather than storage Nevertheless, it is possible that in some patients with cirrhosis and a suboptimal intake of extrinsic factor, there may be a deficient amount of antipernicious anemia factor formed and stored in the liver This might account for a macrocytic anemia with a megaloblastic bone marrow which would respond to liver extract medication

In summary a macrocytic anemia with a normoblastic bone marrow which responds poorly to antipernicious anemia medication is encountered in about two thirds of the patients with cirrhosis of the liver A much smaller number have a microcytic hypochromic anemia due to bleeding from esophageal varices Occasionally a patient with this disorder has a macrocytic anemia with a megaloblastic bone marrow, which responds as well to antipernicious anemia medication as patients with the true addisonian type of the disease Such an anemia may be due to the coincidental association of cirrhosis of the liver with pernicious anemia but more likely as some of these patients have free acid in the gastric secretions, it is caused by a deficiency of the extrinsic factor in the diet The responsible etiologic factors in the commonly encountered macrocytic anemia of cirrhosis with normoblastic bone marrow are not definitely known Such an anemia is not due to hemolysis or hypersplenism although the reticulocytes in the peripheral blood are often increased in number The level of the urobilinogen in the stools is not elevated however and the blood bilirubin is of the direct rather than the indirect type Such an anemia may be due to a combination of deficient extrinsic factor (vitamin B_1) blood loss vitamin deficiencies, including folic acid and vitamin C and to unknown factors

The Macrocytic Anemia Associated with Total Gastrectomy —It has long been known that a macrocytic anemia resembling pernicious anemia may result from various abnormalities of the gastrointestinal tract If Castle s theory is correct then operative removal of the entire stomach should be an ideal experiment for the production of pernicious anemia in humans and possibly in animals While there is some difference of opinion concerning the development of such an anemia in man following total gastrectomy it is unanimously agreed that this type of anemia has never been produced by the total removal of the stomach in animals The discussion of this aspect of the question is presented on page 268

In man observers such as Pack and McNeer (343) state that a macrocytic anemia is rare after total gastrectomy and that when an anemia does develop it is seldom hyperchromic and usually does not respond to liver therapy This is also the opinion of Cameron Watson and Witts

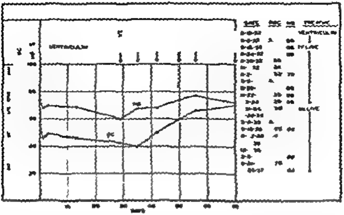

Fig 42 —The failure of response to ventriculin orally and subsequent control by intramuscular liver extract of the macrocytic anemia associated with multiple anastomoses of the small intestine and anastomosis of the ileum with the transverse colon The patient has been kept in perfect health by the continued administration of intramuscular liver extract (Sturgis and Goldhamer courtesy *Annals of Internal Medicine*)

the macrocytic anemia in 23 cases while in 37 strictures were present and in one there were multiple diverticula The strictures were chiefly in the small intestine but six were in the colon Of the anastomoses 15 were entero-enterostomies or entero-colostomies two of which had fecal fistulas in addition and eight were gastro-colic or high jejunal colic fistulae The strictures were tuberculous in 12 in three regional ileitis was present or the ileum had been resected for this condition in some cases the stricture was secondary to adhesions and in others no cause could be found In some of the eight cases where there was a gastro-colic or jejunal colic fistula the anemia might have been in part attributable to the underlying lesion such as peptic ulcer or carcinoma In some patients as much as 60 cm of the small intestine had been resected but it is the opinion of Cameron and his associates (351) that this did not play a role in the production of the anemia as much more extensive intestinal resections in both man and animals are necessary to cause an anemia

The symptoms in the 61 cases of anastomoses and stricture as given by Cameron Watson and Witts (351) were as follows gastrointestinal symptoms present in 52 cases absent in two and not recorded in seven glossitis present in 33 absent in six and not recorded in 22 neurologic disease present in 12 absent in 19 and not recorded in 30 icterus present in 19 absent in 19 and not recorded in 23 macrocytosis present in 49 absent in one and not recorded in 11 "hyperchromia" present in 41 absent in 11 and not recorded in nine poikilocytosis present in 24 absent in none and not recorded in 37 leukopenia present in 35 absent in seven and not recorded in 19 free HCl in gastric juice present in 24 absent in 20 and not recorded in 17

Following a careful study of three patients each of whom had total gastrectomy and after a comprehensive review of the literature MacDonald Ingelfinger and Belding (*347*) concluded that there is a high incidence of macrocytic hyperchromic anemia in patients *surviving total gastrectomy for three or four years* Two of their own three patients developed such an anemia two and five years respectively following total gastrectomy the third had received prophylactic liver therapy A patient has recently been reported by Conway and Conway (*348*) who developed a macrocytic anemia 20 months after total gastrectomy *performed on account of the effects of corrosive poisoning on the stomach* A clinical response occurred following the injection of Vitamin B_{12} but it was suboptimal as compared with what would have been anticipated in true addisonian pernicious anemia The addition of folic acid resulted in a complete hematological remission

In my own opinion a macrocytic anemia amenable to antipernicious medication will develop in a high percentage of patients following total gastrectomy provided (1) *it is known positively that a total gastrectomy was done* (2) that the patient had *not taken antipernicious anemia medication prophylactically* and (3) that the patient *had been observed for a period of at least five years* Even this interval of observation is not sufficient in all patients and an interval as long as eight to 15 years (*345 347*) may elapse before such an anemia appears

Treatment of the anemia associated with gastrectomy is the injection of vitamin B_{12} or the oral administration of 10 to 20 milligrams of folic acid daily Bethell (*349*) prefers the parenteral injection of vitamin B_{12} or liver extract in the same dosage as used in pernicious anemia On the other hand it is reported by Conway and Conway (*348*) that in treating such a patient a greater amount of vitamin B_{12} was required to increase the blood cell count to 3 8 million per cubic millimeter than would have been necessary in a patient with addisonian pernicious anemia and a correspondingly severe anemia Furthermore the red blood cell count in their patient remained at a level of 3 8 millions per cubic millimeter despite a continuation of the vitamin B_{12} treatment until 20 *milligrams daily of folic acid* was added This latter medication caused the red blood cell count to reach 4 6 millions per cubic millimeter within two weeks

Macrocytic Anemia Associated with Anastomoses and Strictures of the Intestines—Since Faber (*350*) reported a case of pernicious anemia associated with an intestinal stricture in 1897 a considerable number of cases of either stricture or anastomoses of the intestines have been reported which confirms the views given in his original presentation

In an extensive review of the literature Cameron Watson and Witts (*351*) have made a study of the clinical features in 61 cases they have collected from the literature in which anastomoses were the basis for

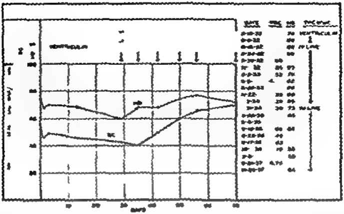

Fig 42 —The failure of response to ventriculin orally and subsequent control by intramuscular liver extract of the macrocytic anemia associated with multiple anastomoses of the small intestine and anastomosis of the ileum with the transverse colon The patient has been kept in perfect health by the continued administration of intramuscular liver extract (*Sturgis and Goldhamer courtesy Annals of Internal Medicine*)

the macrocytic anemia in 23 cases while in 37 strictures were present and in one there were multiple diverticula The strictures were chiefly in the small intestine but six were in the colon Of the anastomoses 15 were entero-enterostomies or entero-colostomies two of which had fecal fistulas in addition and eight were gastro-colic or high jejunal-colic fistulae The strictures were tuberculous in 12, in three regional ileitis was present or the ileum had been resected for this condition in some cases the stricture was secondary to adhesions and in others no cause could be found In some of the eight cases where there was a gastro-colic or jejunal colic fistula the anemia might have been in part attributable to the underlying lesion such as peptic ulcer or carcinoma In some patients as much as 60 cm of the small intestine had been resected but it is the opinion of Cameron and his associates (*351*) that this did not play a role in the production of the anemia as much more extensive intestinal resections in both man and animals are necessary to cause an anemia

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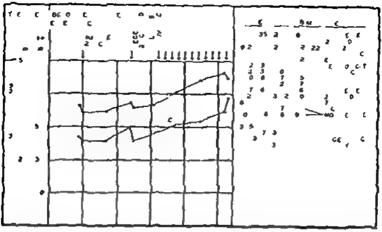

Fig 43 —Patient was 35 year old male who gave a long history of mild abdominal pain flatulence and the passage of frequent soft mushy stools The red blood cell count when the patient was first seen was 2 68 millions per cubic millimeter and the hemoglobin 63 per cent The blood resembled that seen in pernicious anemia as the mean corpuscular volume was 122 cubic microns The patient was operated upon and found to have 4 intestinal strictures in the ileum Improvement in the blood followed but after several months there was a recurrence of the abdominal symptoms and also the anemia This patient represents the occurrence of a macrocytic anemia in association with multiple intestinal strictures causing stasis in the small intestine Resection of the involved part gave only temporary relief It is likely that a similar condition to that from which he first suffered again developed following operation (Sturgis and Goldhamer courtesy *Annals of Internal Medicine*)

In most of these cases the bone marrow had been recorded as simply red and hyperplastic but in eight patients megaloblasts were reported in the marrow *It was the conclusion of Cameron et al (351) that a* megaloblastic transformation may be seen which resembles that observed in pernicious anemia but the change may be of a lesser degree

The anemia which is present with the intestinal lesions is always of the macrocytic type resembling true pernicious anemia with a mean corpuscular volume varying between 110 to 120 cubic microns Occasionally the cell size may be normal or even below normal if there has been a complicating blood loss In about one half of the cases there is free hydrochloric acid present in the gastric secretions which sharply differentiates the condition from pernicious anemia It is reported by Barker and Hummel (352) that the intrinsic factor of Castle was present in one of two cases in which this was investigated

Steatorrhea was present in 10 of the 61 cases reviewed by Cameron and his associates (351) and as they emphasize this may be associated with the etiology of the anemia in these patients

In the treatment of patients with a macrocytic anemia associated with anastomoses or stricture of the intestines liver extract intramuscularly is almost without exception that treatment of choice although folic acid either orally or parenterally 10 to 15 milligrams daily may be effective In the anemia associated with gastrectomy the parenteral

administration of vitamin B₁ or liver extract may be more effective than folic acid in correcting the anemia In patients with diminished intestinal absorptive surface Bethell (349) believes that folic acid is to be preferred to liver extract It is stated by Hall (353) also that folic acid in doses of 10 to 20 milligrams daily is effective treatment in the macrocytic anemia following operative procedures on the intestine

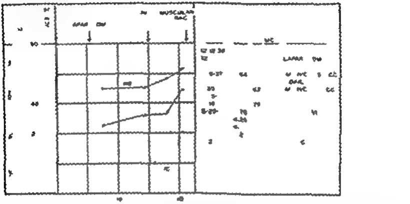

Fig 44—Figure showing a satisfactory hematological response to effective intramuscular injections of liver extract in a patient with ileocolic fistula The condition was thought to be due to an old tuberculous salpingitis with a localized peritonitis but biopsy which was done when an unsuccessful attempt was made to repair the condition showed nothing but chronic infection The patient gained 29 pounds in the fourteen months of treatment (Sturgis and Goldhamer courtesy *Annals of Internal Medicine*)

The question of *surgical treatment* should be considered in every patient with intestinal strictures or anastomoses Not only may this correct the anemia but also it may be indicated in order to relieve the abdominal complaints In the series studied by Cameron *et al* (351) 25 patients were treated surgically Eleven died from the operation in one the operation was technically unsuccessful in five the operation failed to correct the anemia and in eight the anemia was cured Undoubtedly a number of the operations were performed some time ago without the benefit of improved surgical technics which now prevail and would certainly result in a lower mortality rate The following comments are made by Barker and Hummel (352) regarding treatment (1) Without surgical or antipernicious anemia medication the outlook for improvement is poor (2) A high operative mortality is associated with the surgical procedures employed to correct intestinal abnormalities (3) Elimination of the intestinal abnormality may or may not be followed by a complete cure (4) An anastomotic operation designed to circumvent a stricture is less likely to succeed than the resection of a stricture or the restoration of the normal continuity of the bowel when anastomosis is the anatomical lesion (5) Although liver therapy may

control the anemia, it obviously cannot be expected to relieve the symptoms of partial intestinal obstruction (6) Surgical treatment is to be recommended for all patients with strictures and for young patients with anastomoses (7) Liver, vitamin B_{12}, or folic acid therapy alone is indicated for older patients with well functioning anastomoses in whom the operative risk is great

The cause of the macrocytic anemia due to lesions of the intestine is not clear Superficially it is logical to assume that such an anemia is due to a failure of the normal absorption of the antipernicious anemia factor and certainly this may play an important role in some instances Barker and Hummel (352) point out however that following studies of the absorption of fat dextrose and ascorbic acid probably deficient absorption alone cannot explain the development of macrocytic anemia in these patients They suggest that a deficiency of the extrinsic factor may play a secondary role in the causation of the anemia There is no evidence that damage to the liver is of importance in this connection They make the suggestion that as a result of the lesions there may be excessive bacterial activity in the intestinal tract According to them it is possible that such a pathologic change could act by (1) preventing formation of the hemopoietic factor or destroying it or (2) by elaboration of an excessive amount of the toxic products of bacterial putrefaction which cannot be neutralized by the detoxifying mechanisms of the body

It is the opinion of Cameron *et al* (344) that the anemia associated with intestinal disorders is due to stagnation resulting from stenosis or from stagnant loops of intestine In support of this they have produced blind loops in the small intestine of rats and have shown that if these loops are so designed as to be filled by peristalsis a macrocytic anemia develops in many of the animals (354)

ACHRESTIC ANEMIA

The term achrestic anemia from the Greek meaning failure to utilize was introduced in 1935 by Wilkinson and Israels (355) to describe a group of cases which closely resemble pernicious anemia in many respects, but differ from it sharply in certain others as follows (1) free acid is present in the gastric secretions (2) there is a failure to respond satisfactorily to antipernicious anemia therapy and (3) it has been demonstrated that the antianemia principle (erythrocyte maturing factor) is present in the liver

The features of achrestic anemia are described as follows by Wilkinson (356) the changes in the peripheral blood are identical with those of pernicious anemia and furthermore there is a megaloblastic bone marrow There is no involvement of the nervous or gastrointestinal symptoms and no indication of a hemorrhagic tendency toxic factor or liver disease Free hydrochloric acid pepsin and the intrinsic factor

are usually present in the gastric juice. The livers at necropsy contain large amounts of the antipernicious anemia factor but despite this the patients show a progressive and finally a total failure to respond to potent antipernicious anemia medication. It is stated by Wilkinson that the etiological factor is a failure to utilize the antipernicious anemia principle or to mobilize it from the depots in the liver. According to Wilkinson (356) there should be no difficulty in differentiating this condition from aplastic anemia. The latter condition while it may in certain instances have a hyperplastic marrow is *never megaloblastic* as seen in true pernicious anemia and in achrestic anemia. In this observer's opinion achrestic anemia may give a partial therapeutic response to the liver principle, desiccated stomach or folic acid but sometimes it is completely refractory. He believes therefore that the outlook is poor.

A condition similar to achrestic is termed *refractory megaloblastic anemia* by Davidson (357). This observer states that in observing 450 cases of megaloblastic anemia he encountered 59 who were refractory to potent liver extracts. Thirty four of these were associated with pregnancy, the puerperium or the sprue syndrome. The remaining 25 cases of megaloblastic anemia were without obvious cause and hence termed idiopathic megaloblastic anemia. In nine of the 25 patients free hydrochloric acid was present in the gastric juice and certainly these could be classified as achrestic anemia. The patients were of both sexes and ranged in ages from 12 to 76 years. The symptoms and signs were those of a severe anemia. Acute glossitis and neurological involvement were not observed although chronic glossitis was often noted. The spleen, liver and lymphatic glands were not enlarged. The blood and bone marrow changes were identical with those seen in classical addisonian pernicious anemia. The differential diagnosis in those patients with a histamine resistant achlorhydria was impossible from pernicious anemia until it was found that they did not respond to parenteral injections of potent liver extract. The response in these patients was prompt to folic acid and to autolyzed liver extract.

The *treatment* of patients with a condition classified as achrestic or idiopathic megaloblastic anemia should first be with double the usual dose of concentrated liver extract or perhaps vitamin B_{12} although reports of the efficacy of the latter have not been published to date. Probably the most important therapeutic procedure to follow is to administer orally 10 milligrams of folic acid therapy daily in addition to the liver or vitamin B_{12} medication.

MACROCYTIC ANEMIA DUE TO DIPHYLLOBOTHRIUM LATUM

Dibothriocephalus Anemia

The relationship of pernicious anemia to *Diphyllobothrium latum* infestation is not of great importance in North America because the

condition is rarely observed Nevertheless in the large lakes of the north central part of the United States and the nearby provinces of Canada certain varieties of pike and perch are known to harbor the parasite Hence the condition may be transmitted to individuals who are natives of this country and have not been exposed to the infestation elsewhere Its chief interest lies in the theoretical implications which concern this type of anemia, due to a parasite and true pernicious anemia There is no question but that infestation with Diphyllobothrium latum may cause a macrocytic anemia in humans which is identical with that of addisonian pernicious anemia in all respects and one which can be completely cured by the expulsion of the worm

There are, however some important differences between the two diseases namely in tapeworm anemia free hydrochloric acid is present in about 16 per cent of the cases, in some instances in which there is an achlorhydria the acid may return when the worm is expelled the age group is somewhat different for in the infestation in the curve of age incidence there are two peaks one in the third and another in the fifth or sixth decades the disease can usually be cured by expelling the parasite neural manifestations with the fully developed picture of subacute combined degeneration of the spinal cord in the parasitic anemia are rare but they are said to occur

There has been a growing tendency in the United States to consider the association of macrocytic anemia with Diphyllobothrium latum infestation to be a fortuitous situation but this is certainly not correct in all instances It is true that the chance of an incidental association in a country such as Finland where fish tapeworm infestation and true pernicious anemia are both common are great For example Birkeland (358) states that 750 000 persons in Finland are estimated to be infested with this parasite but definite anemia develops in only one of 5000 to 10 000 carriers Furthermore some patients succumb to the anemia even when the worm is removed Also it has been reported that occasionally persons have been cured of diphyllobothrium anemia only to be infested again with the parasite but without the development of an anemia

All of these exceptional cases may be reconciled and understood if one will agree to the following possibilities (1) in some patients there is nothing more than a chance association between the infestation with the parasite in a person with true addisonian pernicious anemia (2) in some other instances the parasite may cause an anemia which is identical with pernicious anemia from the standpoint of the clinical manifestations hematological changes and alterations in the bone marrow and (3) that a certain constitution or hereditary influence in some unknown manner plays an important role in rendering susceptible certain individuals to the action of this worm in more recent years however this is less generally accepted

Fish tapeworm anemia can be cured by expulsion of the worm in most instances by stomach or liver therapy and by folic acid It is von Bonsdorff's opinion (359) that the development of a macrocytic anemia with a megaloblastic bone marrow in any given person who harbors the parasite *results from interference with the interaction between the intrinsic and extrinsic factors* and hence the normal production of the erythrocyte maturing factor Whether or not such an interference occurs in turn depends on (1) the amount of extrinsic factor in the diet (2) the amount of intrinsic factor in the gastric secretions and (3) finally on the location of the parasite in the intestinal tract If it is high in the intestinal tract an anemia occurs If it is low the blood remains normal The theory thus offered by von Bonsdorff (359) affords a plausible basis for the explanation of some of the clinical observation in patients with this infestation For example if the parasite is present but the blood remains normal he suggests it is because the parasite is low in the intestinal tract and consequently does not interfere with the interaction between the intrinsic and extrinsic factors

In a case (360) which I observed at the Simpson Institute the anemia the increase in bilirubin the neurological changes (paresthesia only) the achlorhydria and other clinical features were indistinguishable from those of pernicious anemia A typical hemopoietic remission was induced by the feeding of liver daily before the parasite was removed Although an effort was made to have the patient refrain from eating liver there after she refused to cooperate and was lost sight of before the important observation concerning a possible relapse under these circumstances could be made

Treatment—*The obvious treatment is to remove* the parasite by the usual method with aspidium The patient should then be kept under observation to observe if there is a reticulocyte rise and increase in the red blood cell count to normal If this occurs then it must be assumed that the anemia was due to the parasite and no further therapy is indicated If improvement does not follow expulsion of the worm after a reasonable period then the association between the parasite and the anemia must be considered an incidental one and the proper antipernicious anemia therapy should be instituted

Macrocytic Anemia in Myxedema—Anemia is commonly associated with myxedema According to Lerman and Means (361) in 52 of their patients studied over a period of six years 60 per cent had red blood cell counts below 4 0 millions per cubic millimeter and 52 per cent had hemoglobin values below 70 per cent This incidence corresponds with my experience

The anemia may be of *three types* (1) the most common and the characteristic anemia of myxedema which is a *macrocytic normochromic variety* (2) a hypochromic type due to an associated iron deficiency and (3) a *true addisonian type* of pernicious anemia

The variety of anemia which occurs commonly in patients with long standing and fully developed myxedema is the macrocytic normochromic type It may be present in spontaneous myxedema following total thyroidectomy in man (362) and in experimental animals in which the thyroid has been completely removed (363 364) The red blood cell count usually varies between 3 0 and 3 5 millions per cubic millimeter and the hemoglobin between 9 36 grams per 100 cc (60 per cent) and 10 92 (70 per cent) The color index is usually 1 0 and the mean corpuscular hemoglobin concentration is within normal limits The mean corpuscular volume is regularly at the upper limits of normal or slightly higher usually being between 95 and 105 cubic microns Rarely is the typical anemia of myxedema extreme the hemoglobin ordinarily being no lower than 9 0 grams (58 per cent) and the red blood cell count not lower than 3 0 per cubic millimeter *Anisocytosis is never pronounced and poikilocytosis is not observed* a point to be emphasized in the differential diagnosis from pernicious anemia Although the reticulocytes may be slightly above 1 per cent rarely if ever is there striking evidence of red blood cell regeneration

The observations of Bomford (365) and of Jones (366) indicate that characteristically *the bone marrow is hypoplastic* The latter observer studied the bone marrow by sternal puncture and reviewed previous observations made at necropsy In general he found that the fatty marrow in patients with myxedema was increased at the expense of the red Reference was made to the marrow of thyroidectomized rabbits which has been reported as fatty and hypoplastic It was observed by Jones (366) that the bone marrow in patients with myxedema contained an average of 2 4 per cent of nucleated red blood cells a little more than one third of the normal average Following therapy with desiccated thyroid or thyroxine he noted that there was a marked rise in the percentage of nucleated red blood cells in the sternal marrow

The cause of the characteristic anemia in myxedema is not completely understood as the relation of the thyroid gland to hemotopoiesis is not clearly defined It has been suggested by Bomford (365) that the anemia results from a physiological adaptation to the diminished needs of the tissues for oxygen It is tempting but difficult to prove that the anemia is due to a decreased rate of production of red blood cells associated with a diminished rate of maturation in the bone marrow

This type of anemia responds slowly over a period of months to the administration of desiccated thyroid gland The addition of iron or liver extract in the uncomplicated type is of no value although such medicaments are indicated when certain circumstances prevail as discussed below When treated with desiccated thyroid gland the blood will return to normal within a few months There is no explanation for this long delay in the response to treatment nor is there anything which can be done to expedite it It is of interest to note that when treatment

is instituted there may be wide fluctuations in the red blood cell count and hemoglobin content of the peripheral blood from day to day doubtless due to wide swings in the total blood volume associated with therapy

Since thyroid medication increases the oxygen consumption this means that an additional amount must be transported from the lungs to the body tissues by a circulatory apparatus which is often impaired and a circulating blood which is deficient in its ability to transport oxygen due to its lowered hemoglobin content Caution should be used therefore in the treatment of patients over 50 years of age who have an anemia The total daily dose of desiccated thyroid gland in such patients should be as small as 8 to 32 milligrams and if the anemia is severe several blood transfusions should be given before thyroid therapy is instituted

In addition to the typical anemia of myxedema described above a hypochromic variety may be observed with normal or small red blood cells a color index of less than one and a mean corpuscular hemoglobin concentration varying from 25 to 30 per cent This type of anemia in my experience has almost always been found in female patients and is usually attributable to menorrhagia or metrorrhagia which occur not infrequently in association with this disorder Obviously if hypochromia is present and is due to bleeding with a depletion of iron stores in the body then iron medication in the form of ferrous sulphate 0 3 gram t i d a c is indicated in addition to thyroid medication

A third type of anemia which is observed in myxedema is a macrocytic anemia in association with a megaloblastic bone marrow This does not respond to desiccated thyroid but does to antipernicious anemia medication such as liver extract intramuscularly Undoubtedly in these patients there are two disease processes associated true spontaneous myxedema and addisonian pernicious anemia One of my patients had all of the features of myxedema and in addition had a red blood cell count of less than 500 000 red blood cells per cubic millimeter and all of the other diagnostic criteria of pernicious anemia Furthermore it was not possible to control the anemia in this patient unless both desiccated thyroid and liver extract were administered Similar cases have been reported by Means Lerman and Castle (259) and others It has been generally believed that the two diseases are merely coincidentally associated but with the reports of additional cases the possibility that there may be some etiological relationship must be considered It should be kept in mind therefore that if any patient with myxedema has a red blood cell count below 3 0 million per cubic millimeter and the anemia is of a macrocytic variety the possibility of the two diseases being associated must be considered It should be emphasized also that an achlorhydria occurs in approximately one half of the patients with myxedema (367) When this is considered along with a macrocytic anemia the erroneous diagnosis of pernicious anemia may be made in a patient who has uncomplicated myxedema The lack of a megaloblastic bone marrow and

TABLE XXIV

TABLE SHOWING THE RELATIVE FREQUENCY OF RECORDED SYMPTOMS IN SPRUE

	Percentage
Dyspepsia	96
Asthenia, Weakness Prostration	95
Diarrhea	94
Loss of Weight	94
Carbohydrate and Fat Intolerance	93
Soreness of Tongue and Mouth	92
Anorexia	90
Palpitation and Dyspnea	59
Vertigo and Headache	46
Tenesmus Burning Pain	36
Mucous or Blood in Stools	20
Constipation and Diarrhea	20
Nausea and Vomiting	18
Nervousness Irritability Insomnia	15
Neural Disturbances	14
Salivation	10
Menstrual Disorders	5
Constipation	2

Based on diagram prepared by Rafael Rodriguez Molina (*370*)

neurologic findings the low basal metabolic rate, a high blood cholesterol with failure to respond to potent antipernicious anemia medication should eliminate the diagnosis of *pernicious anemia*

Sprue Classification, Definition, and General Description of the Tropical Variety—Recently Darby (*368*) has classified sprue as follows *Primary or tropical sprue* which exhibits many characteristics of a

TABLE XXV

TABLE SHOWING THE RELATIVE FREQUENCY OF DIFFERENT SIGNS IN SPRUE

	Percentage
Anemia	100
Glossitis and Stomatitis	92
Free HCl Acid	82
Malnutrition Emaciation Cachexia	81
Pallor	70
Skin Changes	64
Edema	40
Pyrexia	36
Abdominal Distention	30
Aphthae	15
Scaphoid Abdomen	12
Nervous Changes	11
Cardio-Vascular Disturbances	11
Icterus	11
Sprue Abdomen	9
Small Liver	4

Based on diagram prepared by Rafael Rodriguez Molina (*370*)

deficiency disease and may be due in part at least to a deficiency of vitamin B_{12} or folic acid According to this observer if this deficiency persists for a sufficient period of time changes may occur in the intestinal tract giving rise to *primary resistant sprue* He regards *secondary sprue or idiopathic steatorrhea* as resulting from changes in the intestinal tract or mesentery which causes malabsorption of various substances including the hematopoietic vitamins folic acid and vitamin B_{12} and hence *resulting in an anemia* Gastrointestinal *defects occurring in infants* may give rise to a state termed *celiac disease* which resembles sprue in many respects The anemia in the latter condition however is usually *of a microcytic hypochromic type with normoblastic bone marrow* but a macrocytic anemia associated with a megaloblastic bone marrow and one which responds to antipernicious anemia medication may be observed

Tropical sprue according to the definition of Rodriguez Molina (*369*) when fully developed is a chronic deficiency state characterized by an insidious onset chronicity of symptoms and progressive development of gastrointestinal disturbances mainly dyspepsia soreness of the tongue and mouth meteorism and diarrhea The stools are usually liquid foamy grayish foul smelling and frequently voluminous and fatty *Stomatitis glossitis* atrophic gastritis and rectosigmoiditis are important findings A macrocytic hyperchromic type of anemia with a megaloblastic marrow accompanies over 90 per cent of the cases fever is present *in about 40 per cent*

No attempt will be made here to describe the syndrome in detail except to present the Tables showing the principal symptoms and signs *of the disease (see Tables XXIV and XXV) (370) to discuss the hema*tology in detail including the response to liver extract folic acid vitamin B_{12} and finally to consider the relationship between sprue and pernicious anemia

Sprue was considered originally to occur only in tropical countries but in more recent years a similar condition non tropical sprue or idiopathic *steatorrhea has been observed in subtropical or even temperate* zones The condition resembles pernicious anemia in that the anemia is identical and hence the general symptoms in the two diseases on this basis are the *same There is also the same type of glossitis* which in sprue may be even more intense and the blood condition responds to liver folic acid and vitamin B_{12} therapy with an increase in the reticulocytes and *number of red blood cells as in* pernicious anemia There are some important differences however as follows the chief complaints in sprue are often pronounced digestive disturbances and especially the passage *of the characteristic stools* the neurological manifestations are usually absent a greater degree of emaciation is more commonly present than is encountered in pernicious anemia and free hydrochloric acid is *found in the gastric secretions of many of the patients*

The Hematology of Sprue.—It is now recognized that in 90 per cent of the patients with this disease, there is a macrocytic anemia which is indistinguishable from that observed in addisonian pernicious anemia. The red blood cell count may vary from a level below 1 million per cubic millimeter to approximately normal, depending upon the stage of the disease. Likewise, reduction in the hemoglobin content of the erythrocytes may vary from 4 to 16 grams (26 to 110 per cent). As in pernicious anemia, the color index is usually high, generally being in the vicinity of 1.0. The mean corpuscular volume is most frequently from 110 to 130 cubic microns, but in some instances it may be much higher than this. Likewise, the mean corpuscular hemoglobin is commonly increased to the vicinity of 40 micrograms. The mean corpuscular hemoglobin concentration in most patients averages about 32 to 33 per cent. From the characteristics given above, it is clear that the findings are similar to those observed in pernicious anemia.

Examination of a stained blood film shows varying degrees of macrocytosis, anisocytosis and poikilocytosis, which changes become more pronounced as the anemia increases in severity. It is unusual, however, to observe bizarre forms of erythrocytes which are so commonly present in pernicious anemia. The leukocyte count is either normal or below 5000 per cubic millimeter, and the same type of multilobed neutrophils are present as are seen in pernicious anemia. Not uncommonly the eosinophils are increased in sprue, but this is thought by some to be due to the frequently associated helminth infestation, for those without such a complication have a normal eosinophil count. In sprue there is usually a reduction in the number of platelets, and the reticulocytes average between 1 and 2 per cent in the untreated cases.

There are very few reported studies of the stomach in patients with sprue, and hence a definitive statement cannot be made concerning the status of the mucosa in the fundus, in which areas the characteristic changes are known to occur in pernicious anemia. In one case of severe chronic and fatal sprue, Cox (*371*) reports that the stomach did not show the characteristic thinning of the mucosa of the fundic zone as in patients with pernicious anemia. This is not in accord with the report of Olleros (*372*) who states that some degree of "gastritis" is present in this disease.

According to Shookhoff (*373*) the macrocytic anemia of the disease may be divided into three types, depending on their reaction to treatment, as follows: (1) those responding to the oral administration of the extrinsic factor, (2) those not responding to the oral administration of the extrinsic factor but yielding to oral liver extract, and (3) those responding only to parenteral therapy. He infers, therefore, that the macrocytic anemia of this disease may be due to a deficiency of the extrinsic factor, a reduction of the intrinsic factor, a failure of adequate absorption of the hematopoietic principle, or a combination of two or all of these mechanisms.

In a very small percentage of cases of sprue the anemia may be normocytic or hypochromic and microcytic It is probably true that in such instances there is an associated iron deficiency which may be due to a diminished intake of iron to impaired absorption or possibly to loss of blood through complicating chronic hemorrhage

Treatment of Sprue with Liver Extract—Following the injection of liver extract there is a striking increase in the percentage of reticulocytes which is followed by a rise in the red blood cells in a manner entirely similar to the changes observed in pernicious anemia when antipernicious anemia medication is given Moreover the patients with sprue experience the same sense of well being the improvement in the appetite the disappearance of the sore tongue and gain in strength as seen in patients with pernicious anemia The gastrointestinal complaints disappear in most instances after the treatment with liver has been continued for several weeks

Treatment of Sprue with Folic Acid—Following the preliminary report of Darby and Jones (*78*) in 1945 and the more recent publication by Darby Jones and Johnson (*374*) in 1946 it has been confirmed that folic acid has a specific effect in sprue (*79 82 375 376*) This is especially true of the anemia but in addition other features of the disease appear to be controlled by this form of therapy

When 10 to 15 milligrams of folic acid is injected daily intramuscularly there is a prompt rise in the reticulocytes to the anticipated peak the hemoglobin and red blood cells increase rapidly to normal levels and the patient displays a great improvement in strength and sense of well being The diarrhea subsides promptly the appetite improves and there is a significant gain in weight With these evidences of improvement there is also a disappearance of the glossitis and the papillae of the tongue regenerate Roentgenograms of the small bowel indicate that the characteristic changes disappear within a short time after folic acid therapy is instituted Although patients with sprue have shown striking improvement following the administration of folic acid at a time when the patient is on a diet devoid of meat and meat products it is emphasized by Spies and his associates (*62*) that a high vitamin high protein diet is of importance in hastening recovery and convalescence

Vitamin B_{12} and Folic Acid in the Treatment of Sprue—It has been demonstrated that vitamin B_{12} when given intramuscularly produces striking general clinical and hematological effects in patients with sprue (*377 378 379 380 381*) The dosage used should be based on the principle that it is better to give an excess than an insufficient amount and hence the same program as employed in the treatment of patients with pernicious anemia may be used namely 10 to 15 micrograms daily for the first week then the same amount three times weekly for the second and third week of treatment and then twice weekly until the blood

is normal Apparently it is not possible in all cases to cause the blood to return to normal and then one must be guided by the possible maximum effect (*381*). More recently Spies and his associates (*301*) have *recommended that these patients be treated with a combination of B_{12} and folic acid* the latter being used in doses of 10 milligrams orally per day

Idiopathic Steatorrhea and Celiac Disease

Relationship to Sprue —In 1888 Samuel Gee first described a condition occurring in England, which he called Celiac Affection as a disease characterized by emaciation and the passage of pale bulky, and offensive stools, observed especially in children Later it was recognized that the condition might be present also in adolescents adults and even in old age The term idiopathic steatorrhea was applied in adults to distinguish it from the steatorrhea which developed from a deficiency of the bile or pancreatic secretions Later, it was determined that there were other manifestations in the condition in addition to emaciation and fatty stools namely infantilism tetany rickets osteomalacia anemias of various types and megacolon

In more recent years, it has been recognized that idiopathic steatorrhea which is now regarded as a term synonomous with non tropical sprue celiac disease and tropical sprue, have much in common and hence can be considered as varieties of the same disease There does not seem to be radical differences between non tropical sprue as observed in temperate climates and tropical sprue, but whether these conditions represent different aspects of the same disease is still a matter of dispute (*382 383*) Furthermore celiac disease as seen in England has many features of sprue and if it occurred in the tropics would probably be called sprue although the latter condition does not commonly have its onset in childhood

According to Hurst (*384*) there are three constant and characteristic features common to sprue, non tropical sprue or idiopathic steatorrhea and celiac disease which require an explanation in any theory pertaining to their pathology They are (1) the stools contain an excess of split fat but no excess of neutral fat meat fibers or starch, (2) the roentgen rays show a disappearance of the normal feathery or herring bone aspect of the duodenum and jejunum produced by the valvulae conniventes and (3) no pathological findings are found after death to explain these changes in the bowel provided postmortem changes have been averted In explanation of these alterations he offers the following theory the characteristic features of the three syndromes sprue idiopathic steatorrhea or non tropical sprue and celiac disease are the result of paralysis of the muscularis mucosae which leads to a loss of the pumping action of the villi into the larger lacteals and to a flattening of the valvulae conni

ventes without change in the normal appearance of the mucous membrane He also suggests that paralysis of the muscularis mucosae may be secondary to a loss of the normal stimulus of Meissner's plexus or to the effect of vitamin deficiency or some toxemia on the plexus This theory is unproven but it is of interest especially because it gives a common explanation to three closely allied conditions He does make an exception to this theory in stating that in a majority of cases of non tropical sprue together with a number of instances of tropical sprue occurring in the tropics and in celiac disease the underlying cause of the condition is obstruction of the lacteals by tuberculous glands and less commonly by Hodgkin's disease lymphosarcoma and metastatic carcinoma Such cases differ from the more usual ones in that the hindrance to fat absorption is at the level of the glands instead of in the villi

Calcium Metabolism —The remarkable changes in calcium metabolism which accounts for osteoporosis and outspoken tetany is due to a loss of calcium from the body in the stools Here it is combined with the unabsorbed fatty acid to form soaps and hence is eliminated

Blood Changes in Idiopathic Steatorrhea and Celiac Disease —A comprehensive study has been made of the blood and bone marrow in patients with the sprue syndrome including non tropical sprue and celiac disease by Innes (385) She concludes that in sprue the characteristic blood picture is a macrocytosis with or without anemia both macrocytosis and anemia being more marked in patients with non tropical than in the tropical group The bone marrow is characteristically megaloblastic when there is a marked degree of macrocytic anemia In some instances the megaloblastic reaction may be completely refractory to parenteral liver therapy but in most patients such treatment will improve the anemia and alter the bone marrow to the normoblastic or intermediate state It is *unusual for the blood to be restored completely to normal* which suggests that some other factor than what is present in parenteral liver extract is necessary for the complete return of the blood to normal in some cases of sprue In some such refractory cases the addition of folic acid has a favorable effect but in others a macrocytic anemia persists despite prolonged therapy with it (386)

Children with celiac disease characteristically have a hypochromic microcytic variety of anemia with a normoblastic marrow It is surprising when the type of anemia is considered that iron therapy orally does not produce a more satisfactory response It is reported by Innes (385) that this may be due to impaired absorption as a response may be obtained by the intravenous injection of saccharated oxide of iron when previous oral preparations have been completely ineffective

The Diagnosis of Non tropical Sprue —Sprue and sprue like states occur in northern latitudes but they are not common and the complicating features are often so prominent they overshadow the underlying disorder

which often may go unrecognized for months or years. It is emphasized by Ingelfinger (387) that the stools in such cases are not always numerous or greasy on gross inspection. The disorganized motor activity of the intestines may occasionally produce symptoms suggestive of organic intestinal obstruction. In other patients the gastrointestinal symptoms may be of secondary importance to certain complications of the condition such as tetany, a tendency to bleed due to diminished prothrombin time or an anemia. Evidence of a deficiency of the vitamin B complex such as a stomatitis or glossitis may or may not be present in non-tropical sprue. Four cases of non-tropical sprue are reported by Ingelfinger (387) in whom the diagnosis was not made for eight months, three years, four years, and fifteen years, respectively, after the onset of the symptoms. According to this observer the diagnosis is not difficult to make, as a simple Sudan III stain is sufficient to determine the presence of steatorrhea. To establish the diagnosis completely, determinations of prothrombin, calcium, and carotin in the plasma, roentgenologic studies of the small intestine, and possibly pancreatic function tests may be necessary. It is suggested (387) that in most instances, however, the clinical picture combining the characteristics of a chronic but non-inflammatory intestinal disorder with anemia and evidences of deficiencies A, D, and K should be sufficient to bring the diagnosis of sprue to mind.

Macrocytic Anemia in Pellagra.—The incidence of a macrocytic anemia in pellagra seems to be in dispute. It was found by Turner (388) that in 50 cases of the malady observed in the southern part of the United States there was an anemia present in only 16 per cent of the cases and in no instance was it macrocytic in type. On the other hand, Spies and Chinn (389) reported that in 30 cases of "alcoholic" pellagra in the northern part of the United States an anemia was present in almost two-thirds of the patients and in more than a majority it was macrocytic in type. If the skin lesions of the disease are disregarded, it simulates the clinical picture of pernicious anemia to some extent, for there is present a glossitis, changes in the nervous system, and diarrhea. Achlorhydria is found in about 50 per cent of the cases.

In a study of 10 patients in Alabama who either showed or had showed the clinical manifestations of pellagra, Moore and his associates (329) found severe degrees of macrocytic anemia. Sternal aspiration indicated a pronounced shift in the bone marrow to the younger red cell elements with a striking increase in megaloblasts. It was concluded that the anemia in these cases was due to both a deficiency in the extrinsic factor and poor absorption from the gastrointestinal tract. This view is supported by the following evidence: (1) it was demonstrated that the intrinsic factor was present in three of the patients, (2) in all instances there was a decided dietary deficiency of animal proteins, (3) six patients responded maximally to 250 grams of beef protein, (4) an alcoholic ex-

tract of beef muscle which was practically free from protein produced a reticulocyte rise and a slight red blood cell increase (5) the crystalline members of the vitamin B complex were given orally and parenterally without effect and (6) after the observations just described intramuscular injections of liver extract produced in nine of the 10 patients a significant increase in the reticulocytes and an acceleration of red blood cell formation It seems clear therefore that a macrocytic anemia is not uncommon in patients with pellagra The cause of this anemia is not a deficiency in the intrinsic factor as in pernicious anemia but the evidence offered by Moore and his associates (329) indicates that it is due to a decrease in the extrinsic factor in the diet and to a malabsorption from the gastrointestinal tract There is a possibility that extensive liver damage may contribute to the macrocytic anemia seen in pellagra In one case dying of acute pellagra with a severe normocytic anemia Sydenstricker and his associates (390) found that the liver contained the antipernicious anemia factor

In a more recent study of 25 patients with pellagra with nutritional macrocytic anemia Moore and his associates (391) found that the erythrocyte count was uniformly under 3 0 millions per cubic millimeter and the blood and bone marrow pictures were identical with those of addisonian pernicious anemia The patients usually had glossitis pellagrous dermatitis cheilosis or peripheral neuritis Hydrochloric acid was almost always present in the gastric juice and the icterus index was normal in most of the patients They concluded that the anemia was due to three causes namely (1) a prolonged deficiency of extrinsic factor in the diet (2) to poor absorption from the intestinal tract and (3) to some deficiency of the intrinsic factor although in the two cases in which tests were made for this it was demonstrated that the intrinsic factor was present All of their patients showed a prompt therapeutic response to parenteral injections of liver extract The presence or absence of a macrocytic anemia in any given patient with pellagra therefore depends to what extent these factors are operating Any one of the three might cause such an anemia but in my opinion the diminished amount of extrinsic factor is probably the most important

It is of interest to note that a patient treated by Hansen Pruss (392) for sprue with a macrocytic anemia later developed the classical skin manifestations of pellagra in association with an obstructing lesion of the stomach This occurred while he was receiving large doses of refined liver extract parenterally over a period of months There was no recurrence of the anemia The sequence of events suggests that refined liver extract does not contain the pellagra preventive factor When the patient was treated with nicotinic acid the clinical evidences of pellagra subsided

Megaloblastic Anemia in Infancy —Although occasional cases of anemia having some of the characteristics of pernicious anemia had been

which often may go unrecognized for months or years It is emphasized by Ingelfinger (387) that the stools in such cases are not always numerous or greasy on gross inspection The disorganized motor activity of the intestines may occasionally produce symptoms suggestive of organic intestinal obstruction In other patients the gastrointestinal symptoms may be of secondary importance to certain complications of the condition such as tetany a tendency to bleed due to diminished prothrombin time or an anemia Evidence of a deficiency of the vitamin B complex such as a stomatitis or glossitis may or may *not be present in non tropical* sprue Four cases of non tropical sprue are reported by Ingelfinger (387) *in whom the diagnosis was not made for eight months three years four* years and fifteen years respectively, after the onset of the symptoms *According to this observer, the diagnosis is not difficult to make as a* simple Sudan III stain is sufficient to determine the presence of steatorrhea *To establish the diagnosis completely* determinations of prothrombin calcium and carotin in the plasma roentgenologic studies of the small intestine and possibly pancreatic function tests may be necessary *It is* suggested (387) that in most instances however the clinical picture combining the characteristics of a chronic but non inflammatory intestinal disorder with anemia and evidences of deficiencies A D and K should be sufficient to bring the diagnosis of sprue to mind

Macrocytic Anemia in Pellagra —The incidence of a macrocytic anemia in pellagra seems to be in dispute It was found by Turner (388) that in 50 cases of the malady observed in the southern part of the United States there was an anemia present in only 16 per cent of the cases and in no instance was it macrocytic in type On the other hand Spies and Chinn (389) reported that in 30 cases of alcoholic pellagra in the northern part of the United States an anemia was present in almost two thirds of the patients and in more than a majority it was macrocytic in type If the skin lesions of the disease are disregarded it simulates the clinical picture of pernicious anemia to some extent for there is present a glossitis changes in the nervous system and diarrhea Achlorhydria is found in about 50 per cent of the cases

In a study of 10 patients in Alabama who either showed or had showed the clinical manifestations of pellagra Moore and his associates (329) found severe degrees of macrocytic anemia Sternal aspiration indicated a pronounced shift in the bone marrow to the younger red cell elements with a striking increase in megaloblasts It was concluded that the anemia in these cases was due to both a deficiency in the extrinsic factor *and poor absorption from the gastrointestinal tract* This view is supported by the following evidence (1) it was demonstrated that the intrinsic *factor was present in three of the patients* (2) in all instances there was a decided dietary deficiency of animal proteins (3) six patients responded maximally *to 250 grams of beef protein* (4) an alcoholic ex

cular hemoglobin concentration indicates a normochromic anemia as this determination is almost always within normal limits a leukopenia and thrombopenia are invariably present The bone marrow pattern is megaloblastic In eight of the 10 cases in which gastric analysis was done following the injection of histamine there was no free hydrochloric acid and the total acidity was usually low In each case which could be studied carefully folic acid and liver extract had a curative effect on the anemia and in most of their cases the blood disorder soon ceased to be the main problem within a short time after therapy was begun The course then became one characteristic of the underlying disorder or associated complication as diarrheal disease pneumonia hepatitis meningitis septicemia and renal involvement In some of their cases the outstanding clinical feature was a protracted irregular fever for which there was no obvious explanation

In the opinion of Zuelzer and Ogden (394) the anemia may be explained on the same basis as the anemia in addisonian pernicious anemia namely as the result of a disturbance in the regeneration of bone marrow cells which limits the production of mature erythrocytes leukocytes and platelets The etiologic factors responsible for such a condition are less clear It may be assumed to be due to a deficiency state of such factor or factors such as folic acid or those present in commercial liver extract

Treatment of Megaloblastic Anemia of Infancy—As previously mentioned it is reported by Zuelzer and Ogden (394) that in each one of their 25 cases in whom the results of treatment could be followed for a sufficient period and were not obscured by the effects of blood transfusions folic acid and liver extract had a distinctive curative effect

Five cases were treated by Sturgeon and Carpenter (395) with a single intramuscular injection of 25 micrograms or less of vitamin B_{12} and in three the response was specific and complete but in two it was equivocal They concluded that vitamin B_{12} is effective therapeutically in some cases of megaloblastic anemia of infancy Furthermore they are of the opinion that its effectiveness is possibly enhanced by adjunct therapy with ascorbic acid

It is reported by Lubby (396) that three patients with this form of anemia did not respond to vitamin B_{12} injections in doses ranging from 100 to 125 micrograms Subsequently they reacted favorably to folic acid therapy

As previously mentioned it is reported by Zuelzer and Ogden (394) that in each one of their 25 cases in whom the results of treatment could be followed for a sufficient period and were not obscured by the effects of blood transfusions folic acid and liver extract had a distinct curative effect

Macrocytic Anemia in Space Consuming Lesions of the Bone Marrow—If one relies upon the mean corpuscular volume which is accepted as the best criterion of presence or absence of a macrocytic type of anemia

reported previously in infancy, megaloblastic anemia of infancy was not established as a distinct clinical entity until the comprehensive study of Rotch and Ladd was published in 1901 (393) They reported the case of an infant nine months old who developed the clinical symptoms and blood appearances of an idiopathic anemia The following points were emphasized as occurring in their patient the insidious onset with moderate and paroxysmal attacks of indigestion the extreme pallor and great loss of strength the absence of any demonstrable cause for a secondary" anemia the slightly elevated body temperature for months, the absence of glandular or splenic enlargement the presence of the typical characteristics of the blood of pernicious anemia the absence of any considerable degree of leukocytosis, the rapid improvement in the general symptoms and in the character of the blood until the infant in all respects appeared absolutely sound and healthy which in itself is typical of the remissions which occur in pernicious anemia

They concluded erroneously that the picture so typical cannot be explained by any other diagnosis than that of pernicious anemia It is of interest to note that such an astute observer as Dr Richard Cabot of Boston then undoubtedly as well versed in hematology as anyone in this country examined the blood films and commented as follows

I believe that the case is in all probability pernicious, and the baby will die within a year Fortunately his diagnosis and prognosis were incorrect and the infant made a complete recovery

The most complete study of the condition is that of Zuelzer and Ogden (394) Based on 25 cases, they describe the clinical picture as having the following characteristics the disease occurs in infants usually between the ages of two to 16 months it is almost always observed in the white race a few are born prematurely the disorder occurs equally in the two sexes most of the infants have a cough coryza or both for several weeks before admission to the hospital and the beginning of the illness is usually referred to these symptoms fever vomiting and diarrhea are common complaints The physical examination usually reveals evidence of a severe anemia as extreme pallor is almost always present There is usually a soft systolic hemic murmur present and the heart may be slightly enlarged the liver is invariably" increased in size but the spleen was palpable in only 10 of their 25 patients adenopathy is not present petechiae were noted in 20 per cent the nutritional status was poor in one half of the patients

The laboratory data as given by Zuelzer and Ogden (394) may be summarized as follows characteristically the anemia is macrocytic and normochromic in type the mean corpuscular volume reaching as high as 156 cubic microns in one patient but in a few instances the anemia is normocytic or the cells occasionally may be less than normal in volume varying from 76 to 96 cubic microns characteristically the mean corpus

globin which responded to the parenteral administration of liver extract In support of this possibility it is stated that the patient had a poor appetite and her weight decreased to 79 pounds her tongue and mouth were sore and the teeth were in such a poor state of repair that mastication was difficult Necropsy confirmed the clinical diagnosis of Hodgkin s disease and showed also pronounced infiltration of the bone marrow in the vertebral bodies

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it should be emphasized that a pronounced macrocytic anemia due to space consuming lesions is not common In most instances in such an anemia the mean corpuscular volume is within normal limits as is the mean corpuscular hemoglobin concentration The color index is commonly in the vicinity of 1 0 The anemia therefore in such conditions is properly described in most instances as normocytic and normochromic In some cases however, the mean corpuscular volume is slightly increased, but ordinarily it does not exceed no more than 100 to 110 cubic microns and there is usually a normal amount of hemoglobin present per cell The impression is often gained, however, when the blood is examined in a stained film, that a very definite macrocytic anemia is present Such an anemia as emphasized by Mettier (*397*) may be present in cases of myelosclerosis, osteosclerosis neurofibromatosis Gaucher's disease carcinomatosis and multiple myeloma The blood picture is characterized by a moderately severe anemia with leukopenia seldom an increase in the white blood cell count, and the presence of myeloblasts and normoblasts in the circulating blood

In my experience this same blood picture may be present in patients with subleukemic leukemia In such patients there may be no palpable lymph glands or splenomegaly in achlorhydria and the abnormal white blood cells in the peripheral blood are often very scarce When such changes are present the differential diagnosis from pernicious anemia may be exceedingly difficult without the aid of a therapeutic trial of antipernicious anemia medication and a sternal puncture

An interesting example of a hyperchromic" macrocytic anemia which occurred in Hodgkin's disease, is reported by Townsend and Braunstein (*398*) From the history however I am inclined to interpret the anemia not as a myelophthisic variety but possibly one which resulted from a deficiency of the extrinsic factor The patient was a 59 year old female who had a severe anemia as indicated by a red blood cell count of 1 3 millions per cubic millimeter a hemoglobin of 50 per cent (7 25 grams) and white blood cell count of 8600 per cubic millimeter a color index of 1 9 a mean corpuscular volume of 140 cubic microns and mean corpuscular hemoglobin of 54 micro micrograms The red cells showed pronounced macrocytosis poikilocytosis and basophilia Free hydrochloric acid was present in the gastric secretions Following the injection of liver extract intramuscularly the reticulocytes reached 19 per cent on the seventh day and there was an increase in the total red blood cell count of 950 000 per cubic millimeter in approximately three weeks The patient succumbed to a bronchopneumonia shortly after the peak of the reticulocytes was reached

There is a possibility that this patient may have had a deficiency of the extrinsic factor This would account for the presence of a macrocytic anemia with a high color index and increased mean corpuscular hemo

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CHAPTER VII

CHRONIC CONGESTIVE SPLENOMEGALY

Banti's Syndrome

Synonyms.—Splenic anemia. Fibrocongestive splenomegaly.

Definition.—This condition is a syndrome resulting from a circulatory disturbance of the spleen usually if not always associated with a hypertension of the splenic vein. It is characterized by chronicity, hemorrhages from the gastrointestinal tract, splenomegaly, a normochromic or hypochromic anemia, leukopenia, frequently thrombopenia, and evidence of a collateral circulation between the portal and caval venous systems. An excellent bibliography of 133 articles dealing with the disease is given in a general article on the condition by Wagley (*1*).

History.—Banti (*2, 3, 4*) described the syndrome named after him as characterized by a marked splenomegaly associated with an increasing and fatal anemia. The spleen was enlarged and had certain vague changes which he considered to be typical whereas the liver showed "all of the characteristics of Laennec's atrophic cirrhosis." He likewise called attention to the "chronic sclerotic endophlebitis" which is "occasionally found *exclusively in the splenic vein*." This latter observation does not seem to have attracted much attention but is now interesting in the light of Thompson's hypothesis dealing with the cause of the disease. The three well known clinical stages of the condition now passe as stated by Banti are 1 the anemic, 2 the transitional, and 3 the ascitic. The first change is the enlargement of the spleen which he claimed precedes all other manifestations. This is followed by the stage of anemia with its characteristic symptoms and finally the third or ascitic stage which is associated with cirrhotic changes in the liver. It was Banti's opinion that the anemia results from "chronic poisoning whose source could lie only in the spleen." Furthermore he believed that the hepatic lesions were the direct result of the changes in the spleen. He has this to say in regard to treatment (*4*): "Since the original seat of the trouble lies in the spleen and since all medicinal treatment is without effect, splenectomy is urgently to be recommended. This is the only therapy even after hyperplasia of the connective tissue in the liver has set in, but the operation should be performed before the beginning of ascites. The operative statistics from the clinic in Florence are favorable because two of the three patients recovered completely and the third died of puerperal complications not connected with the operation."

Banti recognized that he was not the first to report cases of splenic anemia for in his 1898 article he quotes a number including Woillez (5) as describing a progressive anemia in association with a large tumor of the spleen and Gretschel (6) as describing a similar case and introducing the term splenic anemia

It is of interest to note that, in 1904 Dock and Warthin (7) reported two cases with the syndrome of Banti's disease which they preferred to call splenic anemia" In both patients there was calcification and stenosis of the portal vein They conclude their article with the following sentence The two reported cases however, may be taken as further evidence in favor of the view that the symptom complex of splenic anemia represents a group of varying pathological conditions the splenic condition being secondary This is in accord with the ideas advanced by Thompson in more recent years (8)

Etiology and Pathology

Theories Relating to the Cause of the Syndrome—The disease usually appears in the first half of life before the age of 35 years but it may occur in infancy or old age Some claim that it is more prevalent in the female sex but statistics do not support this There is no evidence that heredity plays a role, although more than one case has been known to occur in the same family

Since 1883 when Guido Banti first described this syndrome in his monograph *Dell Anemia Splenica* there has been a controversy concerning the etiology of the condition It is recognized now that all cases are not due to the same cause Banti's original theory that it resulted from the action of some unknown toxic agent first on the spleen and later on the liver is no longer tenable He did however very wisely emphasize that all known causes of splenomegaly as malaria syphilis and others should be eliminated before it was permissible to include it under the name of Banti's disease

Recently Thompson (8) has emphasized that in his opinion this condition is dependent upon a variety of primary lesions *all of which have in common the production of increased pressure in the splenic vein* In a group of his patients in whom the pressure of the splenic vein expressed in millimeters of water was measured at the time of splenectomy there was invariably a splenic vein hypertension The measurements were definitely elevated as indicated by readings which were mostly over 300 and in one instance over 500 millimeters of water, as compared to those with other disease conditions in whom the pressure was over 300 in only one patient and in most cases it was below 200 In all patients with Banti's disease however the splenic vein pressure was well above that in the peripheral circulation which averaged between 125 to 150 Thompson concluded from his observations that there is no

doubt that splenic vein hypertension of great magnitude is an important and invariably present factor in this disturbance"

He divides the obstructive factors into two groups the intrahepatic and extrahepatic and states that there are no significant differences clinical or hematological between the congestive splenomegalies resulting from the various types of obstruction Variations may occur in the speed with which the disease progresses depending upon the nature of the underlying disturbance but the basic pattern is said to be the same in all of the subdivisions The intrahepatic lesion responsible for congestive splenomegaly is cirrhosis which was present in 68 per cent of his 68 cases According to Thompson's belief about 60 per cent of the patients with Laennec's cirrhosis have an associated splenomegaly of the Banti's type and esophageal varices In this group the periportal scars are dense there is great distortion of the intrahepatic vascular bed and minimal evidence of liver cell damage A large number of these patients present the clinical picture of Banti's syndrome and he believes ultimately die of hemorrhage from ruptured esophageal varices In the remaining 40 per cent of the cases of Laennec's cirrhosis less connective tissue less distortion of the vascular bed and more evidence of injury of the liver parenchyma were observed and it is his opinion that these patients are more likely to succumb to hepatic insufficiency with clinical cholemia He states that intermediate stages between these types exist but it is possible to predict with some assurance the degree of splenomegaly in any given case from the microscopic section of the liver *It is likewise concluded by Thompson (8) that if cirrhosis is not present in a patient with chronic congestive splenomegaly at the time of splenomegaly it will not appear subsequently*

Whereas cirrhosis in one half of his cases was the obstructive factor and cause of the portal vein hypertension in the remainder it was attributable to extrahepatic changes and evidence of cirrhosis did not appear even after years of careful clinical study or at subsequent necropsy The extrahepatic lesions responsible for this condition are many and varied in nature Among the causes which have been mentioned are thrombosis of the portal and splenic veins compression of the veins by tumors or scars stenosis of the portal vein and possibly other developmental defects As only four of the younger extrahepatic group observed by Thompson have been studied at necropsy it cannot be said that an obstructive mechanism exists in all such cases In these four however a stenosis of the portal vein was found to be the cause of the portal hypertension The site of the stenosis and its apparent duration suggests that it either occurred before or shortly after birth In a study of 15 cases in whom the non existence of cirrhosis of the liver was proven in all by every means available a special study was made of the extra hepatic factors in congestive splenomegaly by Rousselot (9) The extra

hepatic lesion was demonstrable in the portal venous system of eight of the 15 patients examined. This was recognized at the operating table in four instances and four times it was observed at necropsy. The nature of the extrahepatic lesions responsible for obstruction to the splenic blood in this series is listed as follows:

1	Thrombosis of splenic vein (traumatic)	Case 5
2	Thrombosis of splenic at junction with portal vein (traumatic)	Case 11
3	Thrombosis of splenic vein (nontraumatic)	Case 9
4	Thrombosis of splenic vein (nontraumatic)	Case 14
5	Stenosis of portal vein (upper end) just below liver	Case 4
6	Stenosis of portal vein (lower end) above entrance of splenic vein	Case 12
7	Cavernomatous transformation of portal vein	Case 6
8	Cavernomatous transformation of junction of portal vein and splenic veins	Case 7

According to Rousselot (9) the failure to discover an obstructive factor in the other seven cases is not necessarily a weakness in the hypothesis which considers that splenic hypertension is a cause of the syndrome of Banti's disease but it is due rather to the technical difficulties involving in operative examination of the portal venous bed away from the splenic hilum particularly behind the head of the pancreas. One patient of the series, for example, who had been reported as having an "obstructive factor undetermined" showed at necropsy an obstructive lesion in the portal vein close to the liver. This finding had been predicted because 1 the liver had appeared normal at operation, 2 the red blood cells had been normal between the bleeding episodes and 3 there had been normal liver function tests at the ninth, eleventh and twelfth years after splenectomy.

In a more recent article Rousselot summarizes his experience with the causes of obstruction and portal hypertension resulting in congestive splenomegaly. These observations which are given below were proved either at operation or at necropsy.

I Intrahepatic Causes
- A *Cirrhosis of the Liver*
  - 1 Laennec's cirrhosis
  - 2 Schistosomiasis
  - 3 Biliary cirrhosis
  - 4 Infectious hepatitis

II Extrahepatic Causes
- A *Stenosis of vein*
  - 1 Congenital
  - 2 Acquired
    - Phlebosclerosis

B Compression of Vein

1 Inflammatory cicatrix (following pancreatitis cholangeitis etc)

2 Pancreatic cyst

3 Tumor

4 Aneurysm of splenic artery

C Thrombosis of Vein

1 Inflammatory

2 Traumatic

D Cavernomatous Transformation of Vein

In 30 cases of splenic anemia studied by Kelsey Robertson and Giffin (*10*) portal congestion was found in 28 In 14 of these it was due to chronic disease of the splenoportal veins in 11 it was caused by cirrhosis of the liver and in three the cause was undetermined According to Durham (*11*) all of the accumulated facts indicate that Banti s syndrome is associated with Laennec s cirrhosis in approximately 70 per cent of the cases On the other hand as emphasized by Rousselot (*12*) cirrhosis of the liver results in portal hypertension in only about 20 per cent of the cases As previously emphasized there is also clear evidence to indicate that if cirrhosis of the liver is not present when the manifestations of Banti s syndrome are first detectable it probably will never develop

Not all are in accord with the statement of Thompson that evidence of obstruction of the splenic vein is invariably present in this condition It is stated by Ravenna (*13*) that all of the clinical and pathological signs of splenic congestion can be observed in patients in the absence of an obstructive factor of the portal vessels In his opinion there are changes in the malpighian and other small arteries of the spleen which consist of periarterial hemorrhages and periarterial fibrosis As the result of these lesions he assumes that the function of adjusting the intake of blood in the spleen is altered and as a consequence an increased quantity enters that organ which cannot be discharged through the hepatic resistance under normal conditions Hence the spleen becomes congested and there is an increase in the pressure of the outflowing blood

Although the diagnosis of Banti s syndrome is not made ordinarily when the condition results from a recognizable cause it should be emphasized that the characteristic manifestations of this condition may be produced by a group of known etiological agents The following schema showing the causes of the condition has been suggested by Ravenna (*13*)

A Banti s Syndrome (*of Known Origin*)

1 Infective

a Syphilis

b Leishmaniasis

c Schistosomiasis

d Malaria
e Tuberculosis
2 Toxic
a Alcohol
b Lead
c Phosphorus

B Of Unknown Origin (Primary Fibrocongestive Splenomegaly with Cirrhosis)

1 With prevailing congestion
2 With prevailing fibrosis (Banti's syndrome)

Pathologic Changes in the Spleen—Regardless of the cause the changes in the spleen are the same namely follicular atrophy widespread fibrosis of the pulp with dilated venous sinuses the characteristic perifollicular hemorrhages diffuse siderosis and siderotic nodules On the other hand it is considered by many pathologists that there is no specific lesion found in the spleens of patients with Banti's syndrome For example it is stated by Durham (*11*) that despite a well elucidated clinical understanding of Banti's syndrome the disease process is not generally recognized by pathologists as a pathologic entity

It is stated by Moschowitz (*14*), after a morphological study of 80 spleens in various disorders associated with portal hypertension that the specific splenic lesions associated with this condition should be interpreted as a venocapillary sclerosis He believes that such changes are the result only of portal hypertension but that the histologic changes may be modified by exsanguination infection or cardiac failure There are no "unknown causes for congestive splenomegaly" in his opinion when cases can be submitted to searching postmortem study In other words he believes that his material when subjected to a painstaking examination will show a cause for the portal hypertension in every case

Symptoms and Signs—The onset is usually insidious and frequently the condition has been present for several years before the patient presents himself to a physician for an examination The most common chief complaints are 1 a mass and discomfort in the left side of the abdomen 2 weakness associated with the anemia and 3 hematemesis In a study of 69 patients with splenic anemia Chaney (*15*) found that the complaints could be summarized as follows enlarged spleen and mass in the left side of the abdomen in 29 cases hemorrhages from the stomach in 20 cases weakness in 19 cases indigestion pain in the left side of the abdomen and anemia each constituting the chief complaint in six cases diarrhea in three cases pallor in three cases pain in the epigastrium in two cases shortness of breath in two cases and jaundice in two cases

In general it may be said that the manifestations of the disease mainly are centered about three changes in the body as follows 1 the anemia 2 the enlarged spleen and 3 bleeding from the gastrointestinal tract

The spleen in most instances is moderately to grossly enlarged usually weighing from 400 to 1200 grams in some instances it may reach 3000 grams and extend below the umbilicus

Pain in the upper abdomen is not uncommon but it is usually not a prominent complaint and the patient may not mention it unless questioned specifically on this point It may be due to perisplenitis but this is not common according to McMichael (*16*) It is most frequently explained by the dragging weight of a greatly enlarged viscus In some instances when the pain is in the upper right quadrant it may be due to the changes in the liver

The symptoms associated with the anemia are the usual ones of weakness ease of fatigue pallor dyspnea and palpitation but they are not always pronounced as ordinarily the anemia is not severe unless there has been repeated hematemeses

Gastrointestinal hemorrhages which may manifest themselves by hematemesis or tarry stools or both occur in about one half of the cases These are known to be associated with portal congestion and the formation of a collateral circulation in the region of the lower end of the esophagus The loss of blood is usually large and frequently results in the development of a severe anemia and in some instances in death According to Chaney (*15*) the liver is enlarged in about one third of the cases but in most instances this means that the edge is barely palpable below the costal margin In my experience it is not common to observe a grossly enlarged liver although it is not uncommon to feel the liver edge at the end of a deep inspiration Chaney also states that in his 69 cases of splenic anemia there was found to be cirrhosis in 30 patients but in only 13 of these was the liver found to be enlarged Of the entire series however 30 were found to have an enlarged liver at operation

Ascites as a result of the associated cirrhosis of the liver occurs in about one third of the cases In my opinion this complication is not present unless there is cirrhosis of the liver but all observers are not in accord with this statement

Definite jaundice is rare in this condition but it does occur occasionally A curious sallow brown pigmentation may be observed which resembles the color changes of Addison s disease to some extent

Changes in the Blood and Bone Marrow —The *anemia* may be of the normocytic normochromic type or hypochromic in nature or rarely normocytic and macrocytic It is not difficult to understand why these different changes may occur In the early uncomplicated case the most commonly encountered blood picture is a mild to moderate normochromic normocytic anemia This is usually associated with a leukopenia and often a thrombocytopenia and a hyperplastic marrow The criteria therefore of hypersplenism are met and in my opinion this explains the type of anemia which is then present In many instances however the condi

d Malaria
e Tuberculosis
2 Toxic
a Alcohol
b Lead
c Phosphorus

B Of Unknown Origin (Primary Fibrocongestive Splenomegaly with Cirrhosis)

1 With prevailing congestion
2 With prevailing fibrosis (Banti s syndrome)

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According to Limarzi and his associates (18 19) the bone marrow in the earliest stages shows a myeloid hyperplasia (maturation arrest) They believe that in the advanced stages when cirrhosis of the liver may be present the marrow reveals a marked erythroid immaturity as well as a maturation arrest of the myeloid tissues and an increase in the number of megakaryocytes

Course of the Disease and Prognosis —This condition may pursue a chronic course extending over years without producing disabling symptoms, especially in young persons in whom the disease is most commonly observed At any time however there is a possibility that gastro intestinal bleeding may occur suddenly with hematemesis or tarry stools which may lead to a severe hypochromic anemia or death from hemorrhage In other patients evidence of liver insufficiency or ascites may appear or the signs of portal thrombosis may develop In general it can be said that these patients may live for years and apparently lead a fairly normal existence On the other hand it is not always possible to predict when changes in the patient s condition may occur abruptly with partial or complete disability or death from acute hemorrhage liver insufficiency or intercurrent infection

Treatment —The treatment of this condition is concerned chiefly with the management of the anemia and a consideration of the advisability of splenectomy Following severe bleeding blood transfusions may be necessary in order to save life and to expedite the return of the blood to normal If a hypochromic microcytic anemia develops as the re of the loss of blood then adequate doses of iron should be given in th form of ferrous sulphate 0 3 to 0 6 gram t i d Davidson (20) states that excellent results may be obtained by iron therapy in splenic anemia despite the commonly accepted belief that it is of little or no value When the anemia is of the macrocytic type which may result from an associated cirrhosis of the liver then antipernicious anemia therapy in the form of liver extract injected intramuscularly is indicated

The Indications for Splenectomy —For many years there has been a difference of opinion concerning the indications for splenectomy and its value in this condition This has been largely because 1 the etiology of the disorder has not been established until recent years 2 the selection of cases for operation was not based on clear indications and 3 the mortality from operative procedure has been exceedingly high averaging from 20 to 25 per cent

With a better understanding of the causes of the syndrome and improvement in the surgical technic of splenectomy the place of the operation in the treatment of this disorder is more clearly delineated Removal of the spleen may be of benefit because 1 as the splenic artery supplies 40 per cent of the blood which flows through the portal vein splenectomy may reduce the portal hypertension appreciably ■

tion is complicated by hemorrhage often repeated and severe usually arising from ruptured esophageal varices due to the collateral circulation associated with portal stasis With this complication as is to be expected the blood picture changes to the hypochromic microcytic type On rare occasions the anemia may be of the macrocytic variety *(17)*, due possibly to advanced changes in the liver which lead to an impaired storage of the erythrocyte maturing factor now generally considered to be vitamin B_{12} A further change which tends to make the anemia macrocytic in nature is a striking response compensatory in nature, of the bone marrow to the outpouring of many large reticulocytes as a result of acute hemorrhage

The bleeding time is usually normal unless there is a pronounced thrombocytopenia which is unusual The clotting time is likewise normal despite the reduction in prothrombin of the circulating blood which results from hepatic involvement The erythrocyte fragility tests show no change from normal

The most constant feature of the blood picture is a *leukopenia* which is present in almost all cases although the white blood cell count may be elevated transiently following acute hemorrhage The total white blood cell count is usually below 5000 per cubic millimeter but occasionally is much lower The reduction most commonly affects all types of white blood cells but in some instances the granulocytes are principally involved

The number of *platelets* in the peripheral blood is commonly reduced somewhat below normal but in some instances the count may be below 100 000 per cubic millimeter Occasionally the bleeding time may be prolonged as a result of the thrombopenia but usually both the bleeding and the clotting times are normal as stated elsewhere In the past it has been considered that a normal or an elevated blood platelet count constituted an added risk to splenectomy as following the operation there might be a great increase in the blood platelets and postsplenectomy thromboses result This complication has occurred however when the preoperative blood platelet count was low and it has failed to appear when it was high Although it is logical to assume that a platelet count which is normal or elevated adds to the risk of postsplenectomy thrombosis in my opinion the hazard is not great Furthermore the cautious use of anticoagulant therapy in patients in whom this possibility is more likely would be helpful in controlling the condition

The findings in the *bone marrow* vary with the different stages of the disease In general it may be said that the most common change is the presence of a moderate hyperplasia of a normoblastic type This may be attributable to the hypersplenic basis for the anemia and also as a result of the hemorrhages The presence of a megaloblastic marrow which has been reported as occurring occasionally is probably due to the deficiency of the erythrocyte maturing factor which is associated with the advanced cirrhosis of the liver known to occur in some of these patients

reflecting the better selection of patients and improved surgical technic In this latter period 27 patients underwent splenectomy and of these 17 are still alive but one is in poor condition and several others have been operated upon so recently that the follow up study is inadequate About 40 per cent of the patients have survived the operation for five years and 20 per cent for 10 years It must be concluded from the information at hand that splenectomy in patients with Banti s syndrome rarely cures the disorder to such an extent that the patients are completely restored to health and live a normal span of life In more than one half of the cases however, worth while palliation is accomplished If it is possible to do the combined operation of splenorenal shunt and splenectomy, it is likely that the results will be much better in the future than they have been in the past

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with such a reduction in the venous pressure of the portal system it is possible that an improved circulation through the liver may favor the response of this viscus to supportive therapeutic measures such as a high protein high carbohydrate diet, choline, etc, 3 splenectomy may lessen the tendency to bleed excessively by diminishing the portal hypertension and lessening the pressure in the collateral circulation 4 the operation may eliminate the effects of hypersplenism and result in an increase in the number of erythrocytes leukocytes and platelets of the circulating blood and 5, and by improved function of the liver make more efficient the conversion of vitamin K to prothrombin thereby controlling bleeding which is associated with the hypoprothrombinemia

In the opinion of Rousselot (12) with which I concur splenectomy should always be a part of every surgical procedure designed to relieve Banti's syndrome This operation, with or without a portocaval shunt, should always be considered as a form of therapy in the disease It is recommended that the splenorenal diversion be used if the obstruction is extrahepatic, as the obstructing lesion is most commonly in the portal vein According to Blakemore (21) if the portal vein to inferior vena cava anastomosis (Eck fistula) is employed it is of value principally in patients with cirrhosis

In my own opinion splenectomy in patients with Banti's syndrome is indicated for two main reasons as follows 1 in order to relieve the manifestations of hypersplenism, and 2 to eliminate the portal vein hypertension with its associated complications

Contraindications to Splenectomy—There are a number of distinct contraindications to splenectomy These are given by Durham (11) as follows 1 the operation is rarely justified in patients with progressive decompensating liver disease 2 the operation is contraindicated in his opinion but not in mine in the presence of an increased number of circulating blood platelets as splenectomy will result in a great increase in their numbers and add to the risk of a postoperative thrombosis and embolism 3 the operation is not encouraged unless the bone marrow is hyperplastic as it is only when this condition is present that one may expect the desirable increase in the deficient circulating blood elements and 4 the operation should not be attempted until the red blood cells and hemoglobin content of the blood have been restored to normal levels

Results from Splenectomy—As the operative mortality has been in the vicinity of 20 per cent in the past it has served as a deterrent to its more extensive use When one in five patients succumbs to such a surgical procedure it is necessary to prove beyond the question of a doubt that it will result in certain improvement At the University of Michigan Hospital between the years 1920 to 1934 the operative mortality was 30 per cent but between the years 1935 and 1949 it was 7 4 per cent

CHAPTER VIII

APLASTIC AND ALLIED ANEMIAS

Classification —Under this heading are included those normocytic and usually normochromic anemias which are commonly associated with granulocytopenia and thrombocytopenia They result from an impaired production of erythrocytes neutrophils and platelets due to a hypoplasia of the marrow elements or replacement of them by foreign cells Excluded from this group are all those anemias which are commonly classified as simple chronic anemia and frequently resulting from chronic infection and renal disease among other causes

Admittedly such a classification is arbitrary and necessarily a purely tentative one Furthermore as is true of almost any attempt to arrange diseases in orderly groups there are always exceptions which are either erroneously included or excluded in the various divisions The classification suggested is as follows

Aplastic and Allied Anemias

1 Idiopathic aplastic anemia
2 Secondary aplastic anemia
3 Atypical aplastic anemia
4 Myelophthisic anemia due to Changes in the bones
    1 Osteopetrosis (marble bone disease Albers Schonberg disease)
    2 Myelofibrosis (Myelosclerosis)
    3 Metastatic neoplasm
    4 Leukemia
    5 Plasmocytic myeloma

Idiopathic aplastic anemia is a normocytic anemia associated with granulocytopenia and thrombocytopenia due to aplasia or hypoplasia of the bone marrow without additional changes *Secondary aplastic anemia* is an identical condition but due to some recognizable cause such as benzol poisoning or to the action of other chemicals or drugs Atypical aplastic anemia has been included in this group because the peripheral blood picture may resemble true aplastic anemia The bone marrow however is normal or may be hyperplastic It is probably a form of hypersplenism Myelophthisic anemia is a normocytic anemia due to impaired formation of blood in the bone marrow this results from invasion of the marrow by malignant or other types of foreign cells In all of these conditions the anemia is of the normocytic type and the principal cause

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the anemia without evidence of regeneration of the erythrocytes and at necropsy the outstanding feature would be a complete fatty degeneration of the marrow A complete bibliography to 1911 is given by Hirschfield (7) Sheard (8) in his monograph has covered the literature up to 1923 and had discovered about 125 cases reported up to that time

In 1934 Thompson Richter and Edsall (9) pointed out that cases of so called aplastic anemia all of which had a similar clinical picture could be divided into three types namely 1 those with aplasia of the bone marrow 2 a second group comprising those cases with clinical features similar to the first group but in whom the marrow was normal or even hyperplastic Such cases have been designated as pseudo aplastic anemia to indicate the discrepancy between the findings in the circulating blood and the bone marrow And finally 3 those in which there was evidence of regeneration of the red blood cells in the circulating blood In some of the latter group the marrow is cellular and in other instances the young red blood cells perhaps originate from extra medullary foci The findings reported by these authors emphasize the important point that it is quite possible to have serious interference with the normal process of development maturation and delivery of red blood cells without evident alteration in the cellular content of the marrow

The earliest indication that aplastic anemia may be secondary to a known toxic agent dates to the observations of the action of benzol on the blood by Santesson (1897) who described four cases of the disorder in workers in a rubber tire factory Taking his clew from the clinical observations he exposed rabbits to chemically pure benzene applying it to the skin and by giving subcutaneous injections and by inhalation No adequate hematological studies were made To Selling (*10 11 12*) must be accorded the credit for the first experimental studies of the action of this chemical on the blood of animals He gave rabbits subcutaneous injections of benzene in olive oil and observed only a slight drop in the number of red blood cells but a striking decrease in the number of leukocytes in the circulating blood especially the polymorphonuclear variety In addition he demonstrated that in the animals there was an almost complete aplasia of the bone marrow In 1912 Korányi (*13*) reported the first case of myelogenous leukemia treated with benzol and in the following year the action of the chemical on two patients with polycythemia was reported by Kiralyfi (*14*)

The earliest experiments on the effect of the roentgen rays on the blood forming organs were those of Heineke (*15*) in 1905 Among other things he noted that the red blood cells showed little change despite the fact that there was evidence of increased red blood cell destruction and bone marrow aplasia Early observations on the blood of persons exposed to the roentgen rays were the observations of Jagic Schwartz and Siebenrock in 1911 (*16*) who reported only slight changes in the blood

with the possible exception of hypersplenism is impaired blood production At present in almost all instances the above anemias are refractory to treatment with the possible exception of blood transfusion splenectomy in rare instances and possibly ACTH and Cortisone occasionally

The term refractory anemia as used by Bomford and Rhoads (*1*) has been employed to include anemias of this type Under the designation was grouped (1) anemias which do not yield to any treatment except blood transfusions and (2) those which are not secondary to various recognizable diseases as tuberculosis nephritis cirrhosis of the liver sepsis lymphogranuloma subacute bacterial endocarditis or any other disease of known etiology in which a diagnosis can be made and it is recognized that a causal relationship exists between it and the anemia The objections to the use of the term refractory anemia are that it is too broad as it includes many anemias of different causation and nature and furthermore some of the anemias which have been classified in this group may possibly be benefited by splenectomy, ACTH and cortisone therapy and perhaps other forms of therapy which may be developed in the future

History —The earliest reported case of aplastic anemia is the frequently cited one observed by Ehrlich in 1888 (2) His patient was a 21 year old female with metrorrhagia which had been present 18 days before the onset of the symptoms of the anemia The blood examination as recorded is incomplete and of such a nature as to arouse some suspicion as to its accuracy The red blood cell count for example is given as 230 000 per cubic millimeter the hemoglobin is stated to be "very low" and the leukocytes greatly reduced The neutrophils in the circulating blood were 14 per cent This brief case report was of importance nevertheless because it served to direct attention to a hitherto undescribed form of anemia The significant necropsy findings in this patient were reported as the presence of yellow marrow in the shafts of the long bones with slightly pinkish marrow in the diaphyses There were no megaloblasts normocytes or polynucleated cells and very few normoblasts and myelocytes in the marrow

The disease is not common For example in 1919 Smith (3) was able to collect only 64 cases He concluded that the disorder presents fairly definite clinical features but it may be difficult to differentiate from purpura hemorrhagica and subleukemic leukemia or even from secondary or pernicious anemia at some stages during their course He did agree with Larabee (*4*) that aplastic anemia is not a disease of itself but merely a condition which may arise from various causes

A perusal of the reviews written some years ago by Root (*5*) and by Carey and Taylor (*6*) would lead one to conclude that the disease is an acute uniformly rapidly fatal condition of adolescents and young adults which is associated with a high fever a rather sudden development of

in 1930 (26), and by Loveman (27) The latter author gives a résume of the cases in the literature and states that in 64 cases of post arsphenamine blood dyscrasias in the literature reported at that time there were 30 cases of aplastic anemia with 18 deaths In 1931 Stephens also reviewed the subject of aplastic anemia following arsphenamine therapy (28)

Since the introduction of gold sodium thiosulphate as a therapeutic agent in 1924 by Mollgaard (29 30) it has been recognized that this metal may cause various types of untoward reactions and that in some the hematopoietic functions may be seriously impaired Cases of purpura hemorrhagica agranulocytosis and aplastic anemia have been observed The first case in which there was definite injury to the hematopoietic elements was reported by Emile Weil (31) in 1931 This patient apparently developed thrombocytopenic purpura with a reduction in the total platelet count to 50 000 per cubic millimeter associated with epistaxis hematuria and ecchymoses following the injection of gold in the form of chrysalbine In the years 1931 1932 and 1933 there were several cases of aplastic anemia following gold injections reported by a number of French observers (32 33 34 35 36)

A case of aplastic anemia following the administration of gold sodium thiosulphate for the treatment of lupus erythematosus was observed in 1931 and reported in 1933 by Dameshek (37) The patient succumbed following 18 blood transfusions

The earliest publication relating to Chloramphenicol (Chloromycetin) as a cause of hemopoietic changes in men was made by Volini and his associates (38) In their presentation which was initially made before the Central Society of Clinical Research November 4 1949 in Chicago they reported the case histories of three patients who had been receiving the drug in therapeutic doses and in whom a severe reversible granulopenia occurred in the blood and both erythroid and granulocytic arrest was found in the marrow

IDIOPATHIC APLASTIC ANEMIA

Synonyms —Refractory anemia aleukia haemorrhagica panmyelophthisis hypoplastic anemia toxic paralytic anemia

Definition —This condition is usually an acute or subacute normocytic normochromic anemia arising from an unknown cause commonly combined with a granulocytopenia and thrombocytopenia in association with a hypoplastic or aplastic bone marrow which does not show other changes There is no significant enlargement of lymph nodes the spleen is not palpable and the disease generally pursues a progressively downhill course almost always terminating fatally within a few weeks to a year or more

Etiology —This condition is properly regarded as a rare disease In recent years however it is my impression that more cases are seen

In 1914–1915 Gavazzeni and Minelli *(17)* reported the first case in which there was clear evidence of the development of an aplastic anemia following exposure to this agent. The patient had been in contact with the roentgen rays for a period of 14 years as a worker and died of an anemia. At necropsy the bone marrow was found to be aplastic as regards normoblasts and megaloblasts. The authors considered the condition to be an aplastic anemia resulting from exposure to the roentgen rays. In 1920 Mottram *(18)* reported three fatal cases of anemia which developed after exposure to the roentgen rays. From the description of his cases there does not seem to be any doubt but what they were typical examples of aplastic anemia resulting from exposure to this physical agent. Other publications have also indicated that the x rays *(19)*, radium *(20)*, and radioactive materials *(21)* may be responsible for the typical picture of aplastic anemia.

Prior to the report of Evans in 1916 *(22)* there are no cases in the literature indicating that preparations of arsenic might have an untoward effect on the bone marrow. This observer reported that in a patient with syphilitic aortitis following the injection of one dose of salvarsan there was a severe reaction manifested by dermatitis, hepatitis, nephritis and probably phlebitis. After a second dose was given five days later there was an increase in the large mononuclear cells of the transitional type to a maximum of 54.4 per cent in the circulating blood. The patient had oozing from the gums and one attack of epistaxis with a reduction in the red blood cell count from 5.6 to 3.7 million per cubic millimeter. The bleeding was probably due to the associated jaundice. The earliest report of purpura hemorrhagica following arsphenamine was that of Labbe and Langlois in 1919 *(23)*.

In 1920 Moore and Foley *(24)* reported four cases of patients with syphilis who developed unusual blood pictures following the administration of salvarsan and diarsenol brands of arsphenamine. The reactions were characterized by leukopenia, eosinophilia and increases in the large lymphocyte and transitional groups together with other evidence of destruction of the bone marrow. The fatal case of the group, however, was of unusual interest because, as far as I know, it was one of the first examples of typical aplastic anemia which is recognized as having developed following arsenical therapy for syphilis. In this patient the red blood cell count fell to a low level of 2.97 millions per cubic millimeter and the hemoglobin to 35 per cent. The leukocyte count decreased to 2160 per cubic millimeter with 0.5 per cent neutrophils. At necropsy this patient had an aplastic bone marrow showing degenerated cells and absence of the more mature forms of the myelocyte series. In the same year Gorke *(25)* reported a similar case.

A review of the literature with a consideration of a number of cases which developed a depression of the bone marrow is given by Farley

organs in the gross appear normal except for the anemia aspect and frequently evidence of hemorrhages Bomford and Rhoads (*1*) state that extramedullary hematopoiesis is usually present to some extent and hemosiderosis may be observed According to Rosenthal (*41*) the hemosiderosis apparently indicates evidence of some hemolysis or hemorrhage into the organs Degeneration and necrosis of liver cells which is greater than that attributable to the anemia alone may be present Ordinarily it is considered that the spleen is small in this condition weighing from 35 to 70 grams (*41*) In 14 cases however which included both the idiopathic and secondary varieties Vaughan (*42*) found that it was enlarged in five cases and in two of these it was an outstanding feature In six cases this organ was smaller than normal and in the remainder it was normal in size 3 Usually there are diffuse hemorrhagic phenomena and in some instances this is the most pronounced terminal feature 4 *The bone marrow shows the most characteristic findings in this disease* There is great increase in the proportion of fat cells to hematopoietic cells In some patients all hematopoietic cells are absent with the exception of an occasional small group made up of two or three basophil cells In some patients the marrow may show strands and small collections of cells made up of primary erythroblasts and a few normoblasts almost all with a basophil cytoplasm Occasional myelocytes and mature polymorphonuclear cells are seen The megakaryocytes are entirely absent or greatly reduced in number It is important to note that the distribution of the parts of the bone marrow in which hematopoiesis is obviously impaired is patchy for there may be small portions of very active hemopoietic marrow in an otherwise distinctly hypocellular marrow

Symptoms and Signs —In general the symptoms may be divided into three main types namely 1 those of a severe anemia 2 hemorrhagic manifestations which are associated with the diminution in blood platelets and 3 necrotizing lesions in the mouth throat and other mucous surfaces due to a reduction in the number of polymorphonuclear cells of the circulating blood Both acute and chronic forms of the disease may be encountered In the acute form the condition may be of a fulminating nature in which death occurs within a few weeks to several months The chronic type which appears to be increasing in incidence may run a course of a year or more In some instances its downward trend is interrupted by a period of remission which may persist for several months

The disease usually begins gradually with the characteristic complaints of progressive weakness ease of fatigue pallor dyspnea and palpitation Commonly the general nutrition appears to be fairly well preserved which is compatible with the statement that appetite is maintained and the weight loss in these patients is often not great The pallor

This may be because an increasing number of drugs and chemicals are now known to cause the disorder, and undoubtedly some cases which are regarded as primary in nature are in reality due to some undiscovered etiologic agent

On the other hand idiopathic hypoplastic anemia which is more chronic in nature and milder in degree occurring more frequently in older persons seems to be more common and increasing in incidence It is not proven but generally considered at present that hypoplastic anemia of this type is a milder variety of the more acute variety and that the same etiologic factors are concerned in its causation If this is true there are no known facts to explain why this more chronic form should be caused by the same, as yet unknown, etiologic factors In all such cases extreme care should be taken to exclude various drugs and poisons as a possible cause of the malady

The acute form more frequently attacks persons under 30 years of age and females are generally considered to be more commonly affected than males The hypoplastic type is observed in all age groups

It must be admitted that the etiology of idiopathic aplastic anemia is completely unknown although a number of hypotheses have been suggested It seems clear that the fundamental cause of the anemia is entirely one of decreased formation of red blood cells In the idiopathic type there is certainly no convincing evidence that an increased erythrocyte destruction uniformly plays an important role in the development of the anemia Bomford and his associates (*1*) have suggested that it may be due to poisoning with cyclic compounds of either exogenous or endogenous origin the latter being formed possibly as a result of the failure of the body to detoxify certain substances Others have suggested that it may arise from a primitive and congenitally insufficient bone marrow (39) Hurst (*40*) in 1926 postulated that it might result from the absence of a hormone which regulates the function of the bone marrow *In general it may be said that our knowledge of the underlying cause of this disease is practically nil Although some of the hypotheses are plausible there is no convincing proof that any of them are true Additional information is necessary before any positive statement can be made relative to the cause of this condition*

Pathology —The outstanding pathologic changes are 1 The necrotizing lesions of the mucous membranes especially of the mouth and throat although they may also occur in the vagina and the perianal regions and occasionally in the skin These resemble the ulcerative conditions seen in patients with agranulocytosis and sometimes in lymphatic leukemia Apparently they are due in each instance to a pronounced diminution in the polymorphonuclear cells of the circulating blood which lowers the resistance to infection and permits the ever present pathogenic bacteria on the normal mucous membranes to invade the tissues 2 All

organs in the gross appear normal except for the anemia aspect and frequently evidence of hemorrhages. Bomford and Rhoads (*1*) state that extramedullary hematopoiesis is usually present to some extent and hemosiderosis may be observed. According to Rosenthal (*41*) the hemosiderosis apparently indicates evidence of some hemolysis or hemorrhage into the organs. Degeneration and necrosis of liver cells which is greater than that attributable to the anemia alone may be present. Ordinarily it is considered that the spleen is small in this condition weighing from 35 to 70 grams (*41*). In 14 cases however which included both the idiopathic and secondary varieties Vaughan (*42*) found that it was enlarged in five cases and in two of these it was an outstanding feature. In six cases this organ was smaller than normal and in the remainder it was normal in size. 3 Usually there are diffuse hemorrhagic phenomena and in some instances this is the most pronounced terminal feature. 4 *The bone marrow shows the most characteristic findings in this disease*. There is great increase in the proportion of fat cells to hematopoietic cells. In some patients all hematopoietic cells are absent with the exception of an occasional small group made up of two or three basophil cells. In some patients the marrow may show strands and small collections of cells made up of primary erythroblasts and a few normoblasts almost all with a basophil cytoplasm. Occasional myelocytes and mature polymorphonuclear cells are seen. The megakaryocytes are entirely absent or greatly reduced in number. It is important to note that the distribution of the parts of the bone marrow in which hematopoiesis is obviously impaired is patchy for there may be small portions of very active hemopoietic marrow in an otherwise distinctly hypocellular marrow.

Symptoms and Signs.—In general the symptoms may be divided into three main types namely 1 those of a severe anemia 2 hemorrhagic manifestations which are associated with the diminution in blood platelets and 3 necrotizing lesions in the mouth throat and other mucous surfaces due to a reduction in the number of polymorphonuclear cells of the circulating blood. *Both acute and chronic forms of the disease may be encountered*. In the acute form the condition may be of a fulminating nature in which death occurs within a few weeks to several months. The chronic type which appears to be increasing in incidence may run a course of a year or more. In some instances its downward trend is interrupted by a period of remission which may persist for several months.

The disease usually begins gradually with the characteristic complaints of progressive weakness ease of fatigue pallor dyspnea and palpitation. Commonly the general nutrition appears to be fairly well preserved which is compatible with the statement that appetite is maintained and the weight loss in these patients is often not great. The pallor

This may be because an increasing number of drugs and chemicals are now known to cause the disorder, and undoubtedly some cases which are regarded as primary in nature are in reality due to some undiscovered etiologic agent

On the other hand idiopathic hypoplastic anemia which is more chronic in nature and milder in degree occurring more frequently in older persons seems to be more common and increasing in incidence It is not proven but generally considered at present that hypoplastic anemia of this type is a milder variety of the more acute variety and that the same etiologic factors are concerned in its causation If this is true there are no known facts to explain why this more chronic form should be caused by the same as yet unknown, etiologic factors In all such cases extreme care should be taken to exclude various drugs and poisons as a possible cause of the malady

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of hemoglobin Considering the iron content of hemoglobin to be 0 344 per cent it would mean that 36 74 grams of iron had been given intra venously during this period As there is now good evidence that in the male only traces of iron are eliminated from the body in the urine and through the bile it is likely that this iron which had been given during life accounted for the deposition of the metal throughout the tissues of the body In my opinion therefore, the administration of a large number of blood transfusions may account for the development of the syndrome of hemochromatosis in some patients Whether or not this complication invariably develops in patients with aplastic anemia as a result of blood transfusions is not known It may be as Rosenthal suggests (*41*) that the deposition of iron in the liver and spleen results from hemorrhage or hemolysis in these organs

The physical examination usually shows little if any evidence of weight loss *The most striking feature is an intense pallor without the lemon yellow tint* In less than one half of the patients there is no evidence of abnormal bleeding When present this is usually not conspicuous but is in the form of a few scattered petechiae over the body especially on the legs In about one third of the patients there are retinal hemorrhages which is the commonest sign of an abnormal tendency to bleed in this disorder In some instances however the bleeding may be pronounced not only in the skin but also involving the mucous membranes Ulcerative lesions in the mouth may be present In some patients they are superficial and relatively mild in nature but in other they may be extensive and closely simulate those observed
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In some patients the onset is with hemorrhagic manifestations such as purpuric spots and bleeding from the mucous membranes In others this tendency to bleed may be slight or entirely absent As there is invariably a reduction in the number of platelets of the circulating blood it is remarkable that the bleeding is not more pronounced in all of the patients with this disease Not only may the bleeding be present in the skin and mucous membranes but also from the uterus and into the urinary and gastrointestinal tracts

As the total white blood cell count and the percentage of polymorpho nuclear cells are both reduced in this condition it is not surprising that there should be ulcerative lesions present on the mucous membranes of the body and sometimes even involving the skin They resemble very closely those seen in agranulocytosis Even though the leukocyte count is reduced in practically all patients with this disease ulceration of the mucous surfaces is not always observed but occasionally such change is a conspicuous feature When this is present there are chills fever, pro found prostration dysphagia and aphonia

In the chronic form the patient may develop an amazing accommoda tion to the low red blood cell count and hemoglobin level and apparently experience only symptoms which are far less than one would expect with the existing degree of anemia In one patient whom I observed the hemoglobin averaged between 25 and 30 per cent and the red blood cell count between 1 0 and 1 5 per cubic millimeter for a period of two years but the patient was ambulatory all of this time In addition to traveling rather extensively over the country he even enjoyed swimming as a reation at intervals During this period however his blood was ied by frequent blood transfusions

Occasionally a patient with aplastic anemia may develop evidence of hromatosis as indicated by the appearance of a grayish brown or bronze discoloration of the skin This color is of the greatest intensity in the areas exposed to the light such as the face neck forearms and hands It appears only slightly elsewhere over the body In addition there may be fibrosis of the liver and a deposition of the pigment in the pancreas with an associated diabetes Such a complication of aplastic anemia has been reported by Kark (*43*) in a patient with long standing anemia who had received 290 blood transfusions in nine years Bomford and Rhoads (*44*) state that of three patients with refractory anemia who developed hemochromatosis two had not received an exceptional number of transfusions and one had been given 54 in a period of nine years In one patient of our group in whom hemochroma tosis was observed 137 blood transfusions had been given over an interval of approximately eight years It is estimated that during this time 68 500 cc of blood was injected which is equivalent to 10 686 grams

of hemoglobin Considering the iron content of hemoglobin to be 0 344 per cent it would mean that 36 74 grams of iron had been given intra venously during this period As there is now good evidence that in the male only traces of iron are eliminated from the body in the urine and through the bile it is likely that this iron which had been given during life accounted for the deposition of the metal throughout the tissues of the body In my opinion therefore the administration of a large number of blood transfusions may account for the development of the syndrome of hemochromatosis in some patients Whether or not this complication invariably develops in patients with aplastic anemia as a result of blood transfusions is not known It may be as Rosenthal suggests (*41*) that the deposition of iron in the liver and spleen results from hemorrhage or hemolysis in these organs

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Fever is usually present although its severity varies greatly In most cases it is slight and of an irregular variety but in the fulminating forms of the disease it is high and continuous or septic in type This is particularly true when the necrotizing lesions of the mucous membranes are extensive The heart rarely shows abnormal signs except a hemic murmur it is always normal in size unless a fortuitous cardiac disorder exists which is unusual

It has been emphasized that the *spleen and lymph glands are not often enlarged* (*41*) and this has certainly been true in my experience In fact the presence of enlarged lymph glands and splenomegaly should at once arouse the suspicion that one is not dealing with aplastic anemia but possibly with a subleukemic leukemia of lymphoblastoma of some type It is recognized however that a slight to moderate enlargement of the spleen may be present occasionally in patients with aplastic anemia Never in my experience is the splenomegaly pronounced for when splenic enlargement is present the organ is usually palpable barely

does not have the yellowish tint which is commonly associated with increased blood destruction.

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In the chronic form the patient may develop an amazing accommodation to the low red blood cell count and hemoglobin level and apparently experience only symptoms which are far less than one would expect with the existing degree of anemia. In one patient whom I observed the hemoglobin averaged between 25 and 30 per cent and the red blood cell count between 1.0 and 1.5 per cubic millimeter for a period of two years but the patient was ambulatory all of this time. In addition to traveling rather extensively over the country he even enjoyed swimming as a recreation at intervals. During this period, however, his blood was maintained by frequent blood transfusions.

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of aplastic anemia With the thrombopenia there is a prolongation of the bleeding time frequently for hours the coagulation time is usually normal but there is defective clot retraction

The urobilin excretion the icterus index and serum bilirubin are usually said to be normal but Bomford and Rhoads (*1*) state that in four of six patients in which the test was performed the icterus index was increased as shown by readings which varied between six and 15 These same authors (*1*) report that the fragility of the red blood cells is normal and that free hydrochloric acid was present in five of their 11 cases in which a gastric analysis was done Hydrochloric acid was found however in most of the cases only after alcohol or histamine had been given

Diagnosis—In general the characteristic findings in a patient with aplastic anemia are given as follows 1 an anemia usually profound of the normochromic normocytic type 2 a granulopenic leukopenia 3 a thrombocytopenia associated with purpura and bleeding into the tissues in some cases 4 minimal if any lymphadenopathy 5 splenomegaly usually absent but if present it is slight 6 the reticulocytes in the peripheral blood are generally not increased but in some instances they may be between 2 and 4 per cent 7 there is no increased fragility of the red blood cells 8 the sternal bone marrow shows panhypoplasia affecting all cells 9 there is no history of exposure to toxic substances which might cause such an anemia 10 there is slight if any loss of weight 11 frequently a hypochlorhydria is present and 12 there is no therapeutic response to liver iron or other antianemic therapy and only temporary improvement following transfusions Although all of these characteristics might not be present in any given patient with the disease it can be said that usually a majority of them are

The conditions which might be confused with idiopathic aplastic anemia are secondary and atypical aplastic anemia hypersplenism pernicious anemia idiopathic thrombopenic purpura myelophthisic anemia subleukemic leukemia achrestic anemia and agranulocytosis

Secondary and atypical aplastic anemia can only be ruled out by finding that the disease has resulted from exposure to some toxic agent known to produce such an anemia such as benzol arsenic or the other substances listed under the section dealing with this variety of anemia In atypical aplastic anemia which is probably a form of hypersplenism the only differences are to be found in the bone marrow which in the latter may be normal or actually hyperplastic in nature In both instances the clinical picture may be identical with that of the idiopathic type

Pernicious anemia (*46*) can be eliminated by the fact that the anemia in this disease is macrocytic there is a dramatic response to liver ex

below the costal margin at the end of a deep inspiration Furthermore it is also true that only rarely is there lymph gland enlargement which is sometimes generalized but never striking In some instances this is associated with ulcerative lesions in the mouth and the lymphadenopathy is in the area draining the infected regions

Laboratory Findings —*Blood* —There is almost always a great diminution in the number of red blood cells white blood cells and platelets The hemoglobin content of the blood when the patient is first observed, is usually greatly reduced averaging from 3 0 to 4 0 grams per 100 cc The red blood cell count is most commonly found to be between 1 0 and 2.0 million per cubic millimeter As these figures indicate the color index is usually in the vicinity of 1 0 and the mean corpuscular hemoglobin concentration about 30 per cent or higher The red blood cells are generally normal or slightly increased in size as indicated by a mean corpuscular volume which varies between 96 to 102 cubic microns As the cells usually contain about the normal amount of hemoglobin unless bleeding has been excessive the anemia is normochromic and normocytic in type Although there may be slight alterations in the size and shape of the cells these changes are not conspicuous Usually the reticulocytes are slightly to moderately increased varying between 2 and 4 per cent It is not uncommon to have a few nucleated red blood cells and erythrocytes showing diffuse and punctate basophilia in the circulating blood *That these changes may occur in patients with aplastic anemia is considered by some to be paradoxical but they are readily understood when it is emphasized that extramedullary blood formation may occur and also because patchy areas of active blood formation are not infrequently observed in bone marrow which is otherwise hypoplastic in nature*

The white blood cells are commonly below 3000 per cubic millimeter but they may vary between 1600 and 3500 per cubic millimeter In some instances they may be only 300 to 400 per cubic millimeter The polymorphonuclear cells are invariably reduced their numbers varying between 0 and 40 per cent There may be a "shift to the left" despite the low white blood cell count *Ordinarily there are no myelocytes or myeloblasts present but when such cells are observed one should be suspicious that the patient has subleukemic leukemia rather than aplastic anemia* Apparently it is possible however to have an occasional myelocyte present in the blood of patients with aplastic anemia, and Thompson and his associates (45) report that in 13 cases in whom the clinical diagnosis of aplastic anemia was made myelocytes were found in all instances and in all but three occasional myeloblasts were noted

The blood platelets are characteristically reduced, usually below 60 000 per cubic millimeter but occasionally they have been reported as being present in normal numbers The presence of a normal number of platelets in the circulating blood is evidence against the diagnosis

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tract achlorhydria is invariably present and there is almost always parathesia of the hands and feet and in about two thirds of the patients there are recurrent attacks of glossitis

Idiopathic thrombopenic purpura may simulate idiopathic aplastic anemia very closely The differential points between the two conditions are as follows (1) the anemia of aplastic anemia is profound the red blood cell count often being in the vicinity of 1 0 million per cubic milli meter and the hemoglobin varying from 20 to 30 per cent, the color index is usually high and the anemia is of the normocytic normochromic variety In thrombopenic purpura the anemia is ordinarily not present at the onset of the disease and if it does develop it is the result of acute or chronic hemorrhage Consequently it is of the hypochromic micro cytic type and rarely if ever is it as severe as in aplastic anemia Further more while in aplastic anemia there is often a pronounced leukopenia in thrombopenic purpura the leukocytic count is normal or slightly in creased and there is often a slight shift to the left in the polymorpho nuclear cells

In some instances it is exceedingly difficult to differentiate aplastic anemia from subleukemic leukemia If the leukopenia involves all types of the white blood cells or the lymphocytes primarily one should become suspicious that the patient has subleukemic leukemia or some other form of myelophthisic anemia such as is associated with Hodgkins disease instead of aplastic anemia In subleukemic leukemia the spleen or lymph glands may be enlarged there may be an increase in the number of reticulocytes in the peripheral blood or circulating nucleated red blood cells may be present The anemia in these conditions is normocytic or slightly macrocytic in type and there may be thrombopenia and gran ulocytopenia Sternal puncture in the case of leukemia shows a myeloid hyperplasia or a diffuse infiltration of lymphocytes or monocytes whereas in idiopathic aplastic anemia there is hypocellularity involving all types of cells

The difficulty in differentiating between idiopathic aplastic anemia and aleukemic leukemia in children is emphasized by Sturgeon (47) who suggests that certain volumetric and concentration technics be employed on material aspirated from the bone marrow The findings thus obtained he believes give a decisive quantitative and well defined microscopic pattern It should be kept in mind that the differential diagnosis be tween these two conditions in adults is also often difficult and hence there is a need for new diagnostic measures which would be helpful The methods suggested by Sturgeon may be of assistance but further trials must be carried out before their reliability is established The original publication should be consulted for details of the technics employed

It is possible that the condition might be confused with the syndrome of achrestic anemia described by Israels and Wilkinson (48 49) This

disorder is a macrocytic anemia which resembles pernicious anemia in many respects but does not respond satisfactorily to antipernicious anemia therapy and in some patients there may be free hydrochloric acid in the gastric secretions The chief difference is that the bone marrow changes are similar to those observed in pernicious anemia rather than the alterations characteristic of idiopathic aplastic anemia

In some patients the condition may resemble agranulocytosis for in aplastic anemia the total white blood cell count is almost always reduced sometimes to extremely low levels and the percentage of polymorphonuclear cells is not infrequently below 10 and in some instances these cells may disappear entirely from the circulating blood In such patients also there may be necrotizing lesions of the mucous membrane similar to those seen in primary agranulocytosis In the latter disease however there are several distinguishing points In the first place in agranulocytosis it is uncommon to have an anemia present and it is usually slight when observed Also in this condition the blood platelets are practically always normal in numbers whereas in aplastic anemia they are reduced strikingly in almost every case Furthermore the sternal punctures in the two conditions give different findings In agranulocytosis the granulocytes red blood forming elements and megakaryocytes are usually present in normal numbers in the bone marrow whereas in idiopathic aplastic anemia there is a reduction in all three of the elements Furthermore in agranulocytosis there is frequently a history that the patient has taken some drug known to cause the disease such as aminopyrine gold one of the sulfonamides or other preparations which are of recognized etiologic significance

Course of the Disease and Prognosis —It rarely happens if ever that a patient with idiopathic aplastic anemia recovers from the disease Rosenthal (*41*) states that it runs a progressively fatal course It is reported by Vaughan (*42*) that 89 per cent of his 18 cases succumbed and it is possible that further observation may show that all cases of his may eventually be fatal

The literature to 1939 dealing with recovery in cases of idiopathic aplastic anemia has been summarized by Wintrobe Stowell and Roll (*50*) According to these observers recovery following aplastic anemia is extremely unusual as indicated by the fact that they were unable to find an account of more than six patients who had survived more than a year after the onset of the anemia and even then they could not be considered as having completely recovered Reference to these cases has been made in the above article One of the most remarkable cases is the one reported by Harrison (*51*) This patient survived for nine years and succumbed following a delayed transfusion reaction after having received 290 transfusions This man was found to have a hemochromatosis

TABLE XXVI

Date	R B C	HB (%)	W B C
July 3	1 11	19	3300 P 50% L 43%
July 6	0 85	17	1300
July 8	0 65	14	1050
July 10	0 50	14	1350—T
July 12	0 75	14	2550
July 14	0 59	14	2450
July 16	0 72	20	2150
July 18	0 61	16	2150
July 20	1 36	23	1850—T
July 22	1 37	30	1700
July 24	1 43	25	1550
July 26	1 71	30	700

TABLE XXVI—W S B No 197207 Blood examinations in the case of a 25 year old male with idiopathic aplastic anemia whose complaints were pallor slight weakness mild epistaxis and bleeding from the gums and palpitation for a period of two months Physical examination showed a pronounced pallor of the skin and mucous membranes a systolic murmur and a retinal hemorrhage Without any special treatment except 7 blood transfusions which at the time did not appear to improve his condition significantly he had a period of spontaneous remission with an increase in his red blood cell count to 5 1 the hemoglobin [illegible] [illegible] per cent The patient suffered a relapse however and died about three years after the appearance of his initial symptoms

More recently Minick (52) has reported a case with recovery in a 30 year old male in whom it was felt sure that the diagnosis was idiopathic aplastic anemia The blood findings were characteristic and the sternal puncture showed aplasia of the marrow Treatment consisted of 41 blood transfusions in the first nine months totaling 20 liters of blood Other treatment given was 100 grams of raw liver daily for the first three months a high vitamin diet ferrous sulfate 1 2 grams daily brewers yeast 3 grams daily during convalescence bed rest and nursing care The only unusual finding was a reticulocyte count of between 5 and 10 per cent which persisted for one year Although the first sternal puncture showed aplasia in a second one done about one year later there was a moderately cellular marrow in contrast to the one previously observed

The average duration of the disease varies from a few weeks to slightly over two years although there have been instances in which patients have lived for much longer intervals especially when repeated blood transfusions have been given

Spontaneous remissions have been known to occur in the idiopathic cases and these may persist for several months In one of my patients in whom the hemoglobin was 20 per cent and the red blood cell count below 1 0 per cubic millimeter there was spontaneous improvement with a return of the blood to normal for a period of six months and then a recurrence with a fatal termination

Hemochromatosis has been reported as occurring occasionally in a patient with the chronic form of the disease When this condition has

developed there has been the characteristic cutaneous pigmentation changes in the liver and diabetes associated with the deposition of the iron pigment in the pancreas. Although this complication usually is observed in patients who have received many blood transfusions it has not been established definitely that these are the sole cause of the hemochromatosis. A comprehensive review of the etiologic relationship of hemochromatosis to multiple blood transfusions is given by Schwartz and Blumenthal (53) and an extensive bibliography is included. They suggest that the condition which is designated *Exogenous Hemochromatosis* is the end result of deposition and the subsequent irritating action of the excessive amount of iron in the parenchymal tissues. In their opinion the underlying anemia and the multiple blood transfusions act as predisposing etiologic factor. The relationship of repeated blood transfusions to the development of hemochromatosis is discussed also by Wyatt and Goldenberg (54) and by Zeltmacher and Bevans (55).

In isolated instances a patient with idiopathic aplastic anemia will develop evidence of outspoken leukemia and it has been suggested by some that there may be a close relationship between the two diseases. There is no question but what the clinical picture may be very similar but it is usually possible to differentiate between them by means of sternal puncture. It is my opinion that patients who are suspected of having aplastic anemia and later are found to be suffering from leukemia have had the latter disease in the subleukemic form from the beginning.

In most instances after a variable but usually short period of time the anemia progresses to the point where the patient's resistance is low and a terminal broncho pneumonia results which is the most common immediate cause of death. In other patients the hemorrhagic tendency may dominate the clinical picture and as a result the patient succumbs to bleeding into a vital organ such as the brain or as the result of massive hemorrhage from the gastrointestinal tract. In some instances the picture of a *secondary agranulocytosis* may be the *most important* aspect of the clinical picture and death may be due to sepsis.

Treatment.—The treatment of this condition is usually very unsatisfactory. A careful investigation should be made in each instance for possible toxic agents which might cause a secondary aplastic anemia because the removal of such an etiological agent especially early in the course of the disease may result in recovery.

Blood transfusions are of value for two reasons first because they supply erythrocytes and hence directly combat the anemia second because they may provide blood platelets to a certain limited extent and as a result may control the bleeding. Any effect from blood transfusions must be regarded as usually transitory.

No other form of therapy in my experience has been of proven value. Vaughan (42) has tried blood transfusions intramuscular blood injections bone marrow transfusions (56) iron liver products vitamins yellow

bone marrow pentose nucleotide roentgen ray exposures ultra violet light splenectomy endoglobulin curettement, and sulfonamide drugs He concluded none of the produced evidence of improvement with the exception of blood transfusions which may have prolonged life It seems logical to use sulfadiazine or antibiotic therapy in patients with a low white blood cell count and evidences of sepsis

Splenectomy was done in three patients observed by Rosenthal (57) but no great improvement followed one patient survived for six months and the other two a little over a year Bomford and Rhoads (*44*) state that splenectomy should not be considered in patients with this syndrome In a small group of patients with partly mature cellular marrow and an increased excretion of urobilinogen however they suggest that splenectomy may prolong the effect of transfusions by diminishing the rate of hemolysis It is emphasized by Videbaek and Kofod (58) that certain types of anemia which they include in the aplastic group should be treated with more active measures than they have been in the past Before therapy is administered however it is necessary to determine whether the anemia is due to a purely aplastic bone marrow hypersplenism or space occupying lesions of the bone marrow Even in the case of aplasia or hypoplasia of the bone marrow the authors state the possibility of splenic inhibition of a poorly functioning bone marrow must be considered Hence they believe that it is "worth trying to improve the condition by splenectomy" This procedure should not be done however if the spleen is the seat of pronounced myeloid metaplasia In my opinion in idiopathic aplastic anemia with an aplastic bone marrow splenectomy may be of some temporary benefit but a sufficient number of patients on whom this operation has been done have not been followed for sufficient periods of time to indicate its usefulness *In patients with the so called pseudo aplastic anemia which in some instances may be on the basis of hypersplenism cortisone should first be given a trial If this fails then splenectomy should be given serious consideration*

Atypical Aplastic Anemia —It is appreciated that the characteristic clinical picture and blood changes of aplastic anemia namely a progressive decrease in the number of erythrocytes leukocytes and platelets in the peripheral blood may occur in patients with variable findings in the bone marrow As previously stated experience has shown that alterations in the bone marrow are not always reflected by the findings in the peripheral blood and the failure to correlate the peripheral blood picture with the changes in the bone marrow in this type of anemia is one example in support of this statement It has been proposed by Krumbhaar (59) that the term aplastic anemia be employed for the type of the disease without evidence of regeneration in the blood or bone marrow that pseudo aplastic anemia be used for the variety with a cellular marrow, and that progressive hypocythemia be used to designate the disorder in which there is evidence of attempted regenera

tion in both the bone marrow and the circulating blood Thompson and his associates (9) go even further and urge that the existence of a progressive hypocythemia alone should be sufficient reason for making the diagnosis of aplastic anemia provided subleukemic leukemia can be excluded The term aplastic anemia should be reserved in my opinion for a condition characterized by a hypocythemia of unknown origin in which there is a hypoplastic marrow Atypical aplastic anemia should be employed to designate the condition characterized by a hypocythemia and a normal or hyperplastic marrow In some cases at least this condition may be a form of hypersplenism

The possibility that the changes in the circulating blood and the bone marrow may bear a relation to the prognosis must be considered although further studies concerning this are necessary before a conclusion can be reached Beizer and Watkins (60) state that cases presenting evidence of depression of the activity of the bone marrow and having a relative lymphocytosis followed the usual clinical course of aplastic anemia and death occurred within a short time Those cases in which there was evidence of hyperplasia of the bone marrow and in which a lymphocytosis was not observed did not terminate fatally The length of time however which the latter group was observed was not stated

APLASTIC ANEMIA IN PREGNANCY

It is of interest to note that the first case of aplastic anemia reported by Ehrlich in 1888 (2) occurred in a young pregnant woman Whether the gravid state had anything more than a fortuitous relationship to the anemia is a question which remains unsettled The appearance of such an anemia during pregnancy is not common but it presents a serious complication when it does occur

In 1931 Buze (61) collected 96 cases of aplastic anemia from the literature and of these 47 occurred in women According to Hurwitt and Field (62) additional cases reported in women since that group brings the total to 80 They have analyzed 13 cases of obstetrical interest which are included in that group The authors warn and very properly that in reporting cases of idiopathic aplastic anemia great care must be taken to exclude subleukemic leukemia depression of the bone marrow secondary to sepsis carcinomatosis of the bone marrow and secondary aplastic anemia due to arsenic benzol irradiation and other well recognized causes of this variety of anemia

There is some evidence that pregnancy may be of importance in the etiology of aplastic anemia but it is only suggestive If there is a causal relationship it is apparently rarely evoked as this is an extremely uncommon complication of the gravid state

A survey of the literature by Hurwitt and Field (62) indicates that in pregnant women there is a tendency for aplastic anemia to occur in

the twenties whereas in non pregnant women the average age of occurrence is in the thirties Furthermore these authors report that of 14 cases of aplastic anemia in pregnant women there were nine deaths and five recoveries It is emphasized that all of the recoveries took place after the pregnancies had been terminated either spontaneously or following interference The case of Nieuwenhuis (63) suggests from the sequence of events that a relationship between pregnancy and the aplastic anemia may exist In this patient, the diagnosis of aplastic anemia was made in a woman who was seven months pregnant There was failure to react to all therapeutic measures but a prompt clinical and hematological improvement followed interruption of the pregnancy Furthermore the case of Dobriner Rhoads and Hummel (64) with exacerbations during each of three pregnancies and prompt improvement following interruption of the pregnancies suggests that the pregnancies influenced the anemia to some extent

My previous impression had been that probably a pregnancy should be interrupted in a pregnant woman with aplastic anemia in the hope that the anemia would be benefited Certainly in the presence of such an anemia with the almost constantly associated marked reduction in the platelets of the circulating blood every attempt should be made to correct the abnormal bleeding tendency which is invariably associated This may be accomplished to some extent but never satisfactorily in my experience by repeated blood transfusions They should be employed however to return the hemoglobin and red blood cell count to normal levels Furthermore a trial of cortisone in doses of 75 milligrams orally every six hours should be given for a period of 10 to 14 days in the hope that the platelet count may be increased and the bleeding tendency benefited If the marrow is hypoplastic and the megakaryocytes diminished or absent from the marrow this therapy theoretically would not be of benefit On the other hand it would do no harm and if a sufficient number of megakaryocytes are present in the bone marrow, it might prove helpful Additional observations on the effect of such treatment must be made before any conclusion can be reached regarding its efficacy

In the opinion of Dorgan and McGaughey (65) only the additional analysis of a significant number of cases will decide if the immediate termination of pregnancy is indicated in patients who have idiopathic aplastic anemia as a complication They report a patient who had this condition and underwent spontaneous labor at the thirty eighth week and delivered a normal infant weighing six pounds and 15 ounces The patient however continued to bleed vaginally which eventually led to a hysterectomy Bleeding continued from the nose and gastrointestinal tract and death occurred on the fourth postoperative day

Fanconi Syndrome —This syndrome was first described by Fanconi in 1927 (66) It is characterized by an unusual combination of findings

usually in children as follows: a severe progressive refractory macrocytic anemia and a generalized brown melanin-like pigmentation of the skin associated with a variable type of congenital deformities. The latter have been observed to be microcephaly, changes in the bones, especially of the arms and thumbs, abnormalities of the genito-urinary tract, strabismus, and rarely unilateral deafness, gynecomastia, and congenital heart disease. The condition characteristically occurs in children, but Rohr (67) has reported two cases in adult brothers which he considered to be a variety of the condition.

A case with multiple congenital abnormalities and a hypoplastic anemia with a review of the literature has been reported by Silver, Blair and Kempe (68). It is thought that the disease arises as a result of an inheritable familial trait. Sporadic cases are attributed to spontaneous or chance mutations. The anemia is generally regarded as hypoplastic in nature but there is a possibility that during certain stages there may be a hemolytic element of importance. Treatment is futile in most cases although temporary benefit is derived from multiple blood transfusions and in a few cases it is thought the splenectomy produces temporary but worth while remissions. In these patients splenectomy is most likely to cause improvement if the bone marrow still shows some evidence of active regenerative ability.

Two families have been reported by Estren and Dameshek (69) in which hypoplastic anemia of this type appeared in three of seven siblings of the first family and five of 14 siblings of the second family. They all had apparently the same variety of disorder with peripheral pancytopenia, pallor, weakness and a tendency to bleed. In the cases in which the bone marrow was examined it was found to be hypoplastic. These cases differed from those reported by Fanconi (66) as the hypoplasia was the only familial trait whereas those observed by Fanconi had in addition a number of congenital abnormalities. In one of the patients of Estren and Dameshek splenectomy was done with beneficial results. They likewise believe that in this condition splenectomy should be seriously considered if megakaryocytes are present in the marrow and particularly if platelet production in them can be demonstrated and if the red blood cell elements show some evidence of regenerative activity.

A group of four patients with a hypoplastic anemia have been observed by Palmen and Vahlquist (70) for periods varying from seven to 11 years during which time the blood condition remained stationary at an anemic level for long periods. They believe that this condition is distinct from the majority of cases of aplastic anemia as the onset is early in life, usually during the first year, there is bleeding tendency, the course is comparatively benign and the anemia is fairly well controlled for many years by blood transfusions. Although congenital anomalies were not noted it is possible that such anemias are related to the Fanconi syndrome. One child with this condition reported in the

literature showed a mongoloid habitus and some of the others had a retarded development The authors believe that splenectomy is of possible value and should be tried in refractory cases

Atypical Aplastic Anemia —It has long been recognized that the characteristic blood picture of aplastic anemia may appear in patients in whom the bone marrow is normal or even hyperplastic This finding has been emphasized by Thompson Richter, and Edsall (*9*) and by Bomford and Rhoads (*1*) and others As examination of the bone marrow was not done in many patients before the technic of sternal aspiration was introduced by Arinkin in 1927 much confusion arose from observation of patients during life in whom this information was not available With the more universal use of the sternal puncture technic it became apparent that the changes in the circulating blood and clinical picture in a patient might resemble that of idiopathic aplastic anemia closely but a study of the bone marrow indicated clearly that it was not possible to predict with certainty the state of the marrow which would be found in each patient

As stated by Videback and Kofod (*58*) some patients have been regarded as having aplastic anemia with a normal or hyperplastic bone marrow who have been found to have pancytopenia due to hypersplenism The use of the term atypical aplastic anemia therefore is not applicable in such patients as a wholly different process is involved in producing the changes in the peripheral blood Furthermore the possibility arises in such patients that removal of the spleen may be of benefit and that a trial of ACTH or cortisone therapy is warranted

In such patients the blood picture may be identical with that of idiopathic aplastic anemia the lymph nodes are not enlarged and the spleen is not palpable although it may be possible to demonstrate its enlargement by percussion or by the roentgen ray Certainly the diagnosis of the idiopathic form of aplastic anemia can be eliminated by the demonstration of a normal or hyperplastic bone marrow (For a further discussion of hypersplenism and the changes which it may produce in the circulating blood see page 144)

Aplastic Anemia in Simmonds Disease —Although the part played by the pituitary gland in erythropoiesis is uncertain various types of anemia have been observed in association with pituitary insufficiency The literature dealing with these conditions and the report of a case of aplastic anemia which occurred in a patient with Simmonds disease due to a hemorrhagic cyst is presented by Bloom and Bryson (*71*) The authors were unable to find reference to a previous case of aplastic anemia associated with Simmonds disease in the literature Their patient a female aged 45 years undoubtedly had an aplastic anemia The red blood cell count was 1 13 millions per cubic millimeter and the hemoglobin 3 4 grams with the other changes in the blood and bone marrow characteristics of the disease She also had all of the clinical evidence of Sim

monds disease and a hemorrhagic cyst of the anterior pituitary was found at necropsy. The authors state that the occurrence of Simmonds disease with aplastic anemia may be fortuitous. With the knowledge that the condition is associated with various types of anemia, however, they conclude that it is reasonable to assume an etiological relationship between pituitary insufficiency and the blood disorder.

The "Aplastic Stage" of Various Blood Disorders.—In the past it has been said that various blood dyscrasias had a stage, usually terminal, in which *the bone marrow was in a state of aplasia*. This term has been used in referring to patients with pernicious anemia, leukemia, myelophthisic anemia due to various other causes, erythremia, and other conditions. Its use is not recommended, for such a condition does not represent a stage of true aplastic anemia, and it should not be confused with this clinical entity. It has also been said that severe sepsis, as in pneumonia, septicemia and typhoid fever, may cause aplastic anemia, but this has not been true in my experience. It is acknowledged, however, that a severe infection may cause an anemia of moderate extent or intensify one due to some other cause. For example, if a patient with aplastic anemia did develop an infection, which they often do as a result of the leukopenia, then the anemia frequently becomes much worse in a relatively short time.

The relation of diet to the development of aplastic anemia in humans is not entirely clear. As Bomford and Rhoads state (*44*), hypoplasia of the bone marrow may be produced in animals by the use of deficient diets, and the susceptibility of the hematopoietic system may be conditioned by means of a dietary deficiency in the vitamin B complex. These authors consider that there is, therefore, a rational reason for providing patients who have this disease with a diet which is adequate in all respects.

SECONDARY APLASTIC ANEMIA

Etiology.—It has become clearly established that certain toxic substances may cause the typical clinical manifestations and changes in the blood which are identical with those found in the idiopathic variety of aplastic anemia. In fact, the only differences between the secondary and the cryptogenic types are as follows: in the secondary type, it can be (1) established that the patient has been exposed to a potentially toxic chemical substance, and (2) it is recognized that recovery may occur if the patient is removed from the possibility of further exposure to it.

Although it is generally accepted that certain chemical substances may cause aplastic anemia, it is not always possible to prove conclusively that an etiological relationship exists between the disease state and the potentially toxic substance to which the person is exposed. Most evidence regarding the causes of secondary aplastic anemias is essentially

circumstantial in nature In some instances as is the case in the etiological relationship of benzol arsphenamine irradiation and a few others the evidence although not direct is so overwhelming as to be conclusive The difficulties in proving an etiological relationship may be summed up as follows 1 When a group of persons are exposed to a toxic substance there are variable degrees of susceptibility to it and hence different degrees of involvement In some the reaction may be intense whereas in others it may be slight or entirely absent This probably depends on some unknown inherent trait of an individual which defies analysis and 2 Some persons may possess a native idiosyncrasy toward a drug and hence react abnormally to it while others may develop such a sensitization either as the result of the previous effect of small doses or because a cumulative action occurs as a result of the effect of the substance over a long period of time Finally symptoms may not become apparent at once after exposure to a toxic substance but only after a considerable period of time has elapsed

The only convincing direct proof that any given chemical is responsible for the production of an aplastic anemia is to administer it to a patient or an animal and observe the prompt and constant development of objective changes in the blood This is not feasible in patients but it has been done in the case of animals with certain toxic agents, such as benzol and irradiation Such a method, however, is of no clinical value in an individual patient when one is trying to evaluate the effect of a possible toxic substance to which an exposure is known

Nevertheless when a patient is encountered who has findings of an aplastic anemia it is essential to make a searching inquiry into the possible exposure to substances which might be responsible for the condition This should include questions relating to the use of drugs the nature of the diet, the exposure to substances which might be causative and should include questions relating to the exposure to industrial hazards and the use of toilet and cosmetic preparations Any substance which contains the benzene ring should be regarded with suspicion as should all organic vapors with which the patient may come in contact

Experience has shown that the following agents may be responsible for the production of secondary aplastic anemia

1 Benzol (72)
2 Irradiation (72)
3 Arsphenamine (73)
4 Gold (58)
5 Sulfonamides (74)
6 Dinitrophenol (75)
7 Certain hair dyes (76)
8 Trinitrotoluene (77)
9 Atabrine (78)
10 Thorium dioxide (79)
11 Anti convulsant drugs (80)
12 Chloramphenicol (81)
13 Streptomycin (82)

In addition Bomford and Rhoads (44) regard the following as potentially toxic substances which might be responsible for secondary aplastic anemia hydroquinone creosote resin atophan analgestic drugs such as pyramidon acetanilid phenacetin and a theobromine phenobarbital compound Furthermore it has been claimed by various observers that the following substances may be responsible for the syndrome mustard gas (83) bismuth (84) mercury (85) colloidal silver (85)

Aplastic Anemia Due to Benzene (Benzol) Poisoning —Crude benzene (C_6H_6) is a substance derived from coal tar and differs from benzine a petroleum distillate The former is an excellent solvent for rubber resins fats gums and alkaloids and hence has been employed in many industries such as the manufacture of artificial leather enamels rubber lacquers shellac waterproof fabrics paint removers gilding liquids in electroplating lithographing and photography drycleaning and feather processing The liquid is highly volatile and poisoning usually results by inhalation It is now recognized that toxic effects from this chemical are possible even when the best of preventive measures are utilized Hence close supervision of all workers exposed to this substance is imperative Until some substitute can be found for this valuable solvent the possibility of poisoning of all individuals exposed to its fumes must be kept in mind Comprehensive reviews dealing with the subject have been published by the British Industrial Health Research Board (86) and by Hamilton (87)

The development of benzene poisoning in a given person who is exposed to such a hazard depends upon (1) an individual susceptibility (2) the duration of exposure and (3) the concentration of the fumes There is no proof as has been claimed by some that young women are more susceptible to the chemical or that a person may become acclimatized or develop some vague type of immunity to it as a result of a long but light exposure Furthermore it is now recognized that the manifestations of benzol poisoning may not appear until some time after exposure to the hazard has ceased

The predominating symptoms of benzene poisoning are ease of fatigue and weakness headache dizziness nausea and anorexia nervousness pallor dyspnea palpitation and hemorrhagic manifestations such as bleeding gums epistaxis and menorrhagia

The Blood Changes in Benzol Poisoning —It has long been taught that a reduction in the number of the polymorphonuclear cells of the circulating blood is one of the earliest and most reliable signs of early benzene poisoning but our present knowledge tells us that this is not necessarily true (88) While the typical blood picture in benzol poisoning is characterized by leukopenia with neutropenia thrombopenia and some anemia recent studies have shown that many cases present wide variations from this picture It is now known that chronic exposure may be responsible for varied hematological pictures Anemia which is

usually normocytic or slightly macrocytic may be present but occasionally it is microcytic The color index is usually about 1 0 and slight anisocytosis and poikilocytosis are present A leukopenia thrombopenia and reticulocytosis may or may not be present The bone marrow in the early stages may be hyperplastic and this may account for the presence of myelocytes and irritation forms in the circulating blood As the marrow becomes aplastic the first indication of this in the peripheral blood is the development of a leukopenia Thrombocytopenia appears next and anemia is the last to be observed since erythrocytes have the longest life of all the formed elements of the circulating blood

It is concluded by Valentine (*89*) that the early hematologic changes foretelling the future development of secondary aplastic anemia due to industrial hazards such as benzol are poorly delineated and their interpretation open to much confusion The classical triad of anemia, leukopenia and thrombocytopenia represent a late and severe form of poisoning Even leukopenia alone probably represents such a late stage that it should not be permitted to develop Other changes in the blood are inconstant and vague and hence cannot be considered diagnostic Nevertheless these minor abnormalities represent the only alterations which point to the suspicion of early damage to the hematopoietic system Macrocytosis leukocytosis eosinophilia elevation of the erythrocyte count and the presence of irritation forms of leukocytes in the circulating blood should be regarded with suspicion if the individuals are exposed to noxious agents Any departure in the blood from normal should be regarded as a warning A single or even small number of examinations in which such abnormalities are found particularly if control examinations of the individual in question have not been made are of little value A trend in the hematologic changes as indicated by a series of observations carries a great deal more weight

A case of thrombocytopenic purpura due to benzol poisoning is reported by Vaughan (*90*) and the literature bearing on this subject is discussed He makes the point that depressed platelet production is a commonly associated phenomenon in benzol poisoning but cases of thrombocytopenic purpura *unassociated* with striking changes in marrow elements are rarely found Although the evidence suggests that benzol may have been responsible for the patient s condition such an etiologic relation has not been established beyond the question of doubt

A summary of the hematological findings in nine cases of benzene poisoning as determined by Erf and Rhoads (*91*) is as follows the hemoglobin varied from 47 to 81 per cent and the erythrocyte counts from 1 8 to 4 1 per cubic millimeter A leukopenia was present in all patients as indicated by white blood cell counts which varied from 1750 to 6500 per cubic millimeter The polymorphonuclear percentages were usually normal or only slightly decreased but in one patient only 7 per

cent was present Thrombocytopenia was uniformly present with platelet counts varying from 18 000 to 160 000 per cubic millimeter In all patients the reticulocytes were elevated between 3 8 to 14 per cent The fragility of the erythrocytes in hypotonic salt solutions was normal except in one of the nine cases Varying degrees of anisocytosis and poikilocytosis were present in all of the patients The color index varied from 1 1 to 1 5 in seven of the nine patients The mean corpuscular volume was increased (94 to 111 cubic microns) in all but two These observers found that the sternal marrow in eight patients revealed changes which varied from a hypoplasia with a left shift of the cellular elements to a hyperplasia with normal maturation

An excellent summary of the blood findings in a group of 332 workers exposed to benzol in the photogravure printing industry in New York City has been reported by Goldwater (92) In 100 of these a complete set of hematological observations were made Each individual of the group had been exposed to a concentration of benzol fumes ranging from 11 to 1060 parts per million for a period of at least six months and in most instances for about three years A summary of his conclusions is as follows

1 The abnormalities most frequently observed were anemia, macrocytosis and thrombocytopenia In 84 8 per cent of the group the hemoglobin values were within normal limits Subnormal amounts of hemoglobin were found only in those cases in which there was evidence of severe injury to the hematopoietic system In general it is present only when the erythrocytes have fallen to a low level It was observed that the hemoglobin levels remained relatively high in relation to the red blood cell count in other words the color index and the mean corpuscular hemoglobin concentration usually were high It was found that 47 9 per cent of the workers had red blood cell counts below 4 5 millions per cubic millimeter and in 18 9 per cent they were below 4 0 millions per cubic millimeter Of considerable importance is the observation that in this series of patients the mean corpuscular volume was increased above normal (95 cubic microns) in 46 7 per cent of the workers The following is an analysis of the group with an increased mean corpuscular volume

Size of the Red Blood Cells (cubic microns)	*Per Cent of Workers*
95–99	14 6
100–104	15 5
105–109	7 8
110–114	6 9
115–119	1 9

The mean corpuscular hemoglobin concentration was normal in 88 6 per cent of all cases that is the readings in this group fell between 30 and 35 per cent which would indicate a normal concentration of hemoglobin in the erythrocytes

2 Of considerable importance was the reduction in the number of blood platelets in the circulating blood in patients exposed to benzol In this group it was found that 32 7 per cent had less than 100 000 platelets per cubic millimeter and only 6 per cent had counts of 200,000 per cubic millimeter or greater In a control group of 81 workers, not exposed to benzol there was no count less than 100,000 per cubic millimeter and in 60 per cent of the workers the platelets were above 200 000 per cubic millimeter The difference between the two groups was sufficient to emphasize that a diminution of thrombocytes is an important variation from normal in persons exposed to benzol

3 The findings in this group in regard to the changes in the leukocytes is of importance because in the past leukopenia has been considered to be one of the most characteristic changes observed in benzol poisoning In the group studied by Goldwater only 14 5 per cent had less than 5000 white blood cells per cubic millimeter and 69 per cent had more than 6000 per cubic millimeter In 7 9 per cent the count was between 4000 and 4999 in 4 8 per cent it was between 3000 and 3999 and in 1 8 per cent it was between 2000 and 2999 per cubic millimeter These findings are in accord with the statement of Hamilton who said if the physician depends on a leukopenia for a diagnosis and fails to make a count of the red cells the patient may be fatally poisoned before he discovers that benzol poisoning has caused marrow aplasia

In the group studied there was no evidence of a decrease in the neutrophils but on the contrary there was a tendency toward lymphopenia as compared to the control group For example the incidence of lymphocyte values between 20 and 30 per cent the traditional normal in the benzol group was nearly three times as great as in the control group whereas values above 40 per were twice as frequent in the controls According to Goldwater (92) these findings can only lead to the conclusion that exposure to benzol produces if anything a relative lymphopenia In his series of cases moreover lymphocytosis was not found even in those cases with evidence of severe damage to the hematopoietic system According to this observer it would seem that a frank relative lymphocytosis occurs with some frequency only in the cases of benzol poisoning which terminate fatally with a fully developed picture of aplastic anemia

Other observations made in this study were that (a) monocytosis eosinophilia and basophilia were not found in the benzol group (b) prolongation of the bleeding time was rare and did not follow the reduction in platelets (c) prolongation of the coagulation time was rare (d) the erythrocyte sedimentation rate was apparently not changed in patients with benzol poisoning and (e) the fragility of the erythrocytes did not appear to be altered in benzol poisoning but there did seem to be a slight elevation of the serum bilirubin

It is widely accepted that the anemia leukopenia and the thrombopenia result from a diminished rate of formation of these elements in the bone marrow This is supported by the findings in the bone marrow in the advanced stages of the disease at which time it is aplastic In the early stages however the marrow is hyperplastic

There is some indication that an increased destruction of erythrocytes may be of importance in this condition This is substantiated by the increased rate of excretion of urobilinogen an elevated level of serum bilirubin poikilocytosis and reticulocytosis As pointed out by Erf and Rhoads (91) all evidence of increased hemolysis disappears in almost all patients when they are removed from exposure to benzene Hence they attribute clinical improvement to the cessation of the destructive process as well as a restoration of normal hematopoiesis

It is of interest to note that occasionally a patient with benzene poisoning develops a leukemia This was true of one of the cases observed by Erf and Rhoads (91) The literature concerning this association has been summarized by Selling and Osgood (93) who cite six cases in which leukemia was observed one being of the lymphoid and the others of myeloid types The relative rarity of both benzene poisoning and leukemia suggests that the association is more than fortuitous In such cases however the possibility must be kept in mind that the changes in the peripheral blood resembling those of leukemia might be due to injury of the bone marrow by benzol and a resultant myeloid metaplasia of the spleen (See page 660)

Treatment —The most important aspect of treatment obviously is to prevent the exposure of persons to benzene fumes This is complicated by the fact that persons have a variable susceptibility and hence it is doubtful as to whether there is a safe exposure to the inhalation of this volatile solvent for all persons As Hunter (94) states "it would seem that the only real safe concentration (in the blood stream) is zero" Once the damage to the hematopoietic organs is done complete recovery may occur if the condition has not proceeded to the point when the action is irreversible Although raw and cooked liver liver extract and ventriculin have been used in the treatment of this condition it has not been demonstrated that they are effective forms of therapy Likewise thiamin iron and ascorbic acid have been given but the improvement which follows is probably not related to any of these substances Blood transfusions are undoubtedly of value and if signs of infection are present which may be associated with the granulocytopenia then the use of the sulfonamide drugs should be considered

THE EFFECT OF ROENTGEN RAYS AND RADIOACTIVE SUBSTANCES ON THE BLOOD AND BLOOD FORMING ORGANS

Introduction —The biological effects produced by the roentgen rays and radium are dependent upon ionization which is induced by these

agents in the tissues. Such changes may be produced by the action of x rays and gamma rays, fast and slow neutrons, and beta and gamma particles. The penetrating ability of these rays varies widely and therefore such characteristic must be taken into account when their therapeutic effects are evaluated. For example, the alpha rays produce little effect because they do not travel more than a maximum distance of 40 microns. Nor do the beta rays have much penetrating ability for they are about one half absorbed by 1 millimeter of soft tissue. On the other hand, gamma rays and x rays and fast neutrons have the power of producing ionization through many centimeters of body tissues. It is obvious from this statement, therefore, that the gamma rays and the x rays are of the greatest use in clinical radiation therapy.

Variation in Sensitivity of Body Tissues to Radiation.—Of great importance is the striking difference in sensitivity of the tissues of the body to ionizing radiation. According to Warren and Dunlap (95) and to Henshaw and Snider (96) the following indicates this variation in the body tissues in order of decreasing sensitivity:

1. Lymphocytes
2. Erythroblasts
3. Germinal epithelium of testes
4. Myeloblasts
5. Epithelium of intestinal crypts
6. Germinal cells of ovary
7. Basal layer of the skin
8. Connective tissue
9. Bone
10. Liver
11. Pancreas
12. Kidney
13. Nerve
14. Brain
15. Muscle

Of interest also is the great difference in the size of the lethal dose in different animal species. For example, according to Prosser (97) and to Ellinger (98) the guinea pig will succumb to 175 to 250 r, whereas a lethal dose in man is about 450 r. The rabbit, on the other hand, has a lethal dose of 800 r.

Mechanism of the Effects of Radiation on the Body.—This problem is being studied intensively and any statements which are made at present must be regarded as purely tentative and subject to revision when additional information is made available. According to Jacobson (99) "absorption of radiation in cells and fluids of the body is attended by release of energy. This release of energy is considered by many authorities to consist of transient ionization of water molecules followed by the formation of hydrogen peroxide and chemical radicals which in turn inhibit or denature the sensitive enzymes of enzyme systems."

The effect of irradiation is discussed by Warren and Bowers (100) who quote a number of investigators and emphasize that the sequence of events which occur when ionizing radiation penetrates a tissue are (1) physical, (2) chemical and (3) biological. In other words, there is first a physical absorption of the ionizing radiation by the molecules of

the human tissues This is followed by a series of chemical changes which at present are of an obscure nature And finally there are those pathological effects which result from the physical and chemical reactions These affecting the most sensitive tissues first result in the characteristic pathologic changes

The Effect of Radiation of Hematopoietic Tissue—A survey of the literature indicates that either the alpha or gamma rays may cause a complete aplasia of the bone marrow which involves the leukoblastic erythroblastic and thromboblastic tissues Not always are all three elements necessarily affected at once for they may be involved singly or in combination

With gamma radiation the lymphocytes are first affected Evidence of marrow damage may be observed as early as 24 hours following exposure to the rays evidence of aplasia is most commonly observed in from three to five days with a maximum change appearing on the ninth to the tenth day In general it may be said that the earliest changes are those of a degenerative nature affecting the nuclei later the cytoplasm becomes paler The experiments of Shouse Warren and Whipple (*101*) in which dogs were subjected to radiation over the skeleton illustrate the profound effects which are produced on the blood and blood forming organs by such an agent They observed that fatal intoxication followed the administration of heavy doses Such exposures to the roentgen ray produced a depletion of all the cells of the bone marrow except the connective tissue and fat cells blood vessel endothelium phagocytes filled with brown granules and occasional normoblasts A striking leukopenia characteristically appeared five to six days after exposure and was maintained in the peripheral blood (200 white blood cells or less per cubic millimeter) for the two or three days prior to death

It is of interest to note that massive colonies of bacteria were present in lung tissue of the experimental animals and that there was total lack of tissue and white blood cell reaction to such a bacterial invasion

Another characteristic effect of the roentgen rays is a sudden destruction of the nuclei of the lymphocytes throughout the body The initial changes which may occur within two or three hours following exposure is characterized by nuclear disintegration with phagocytosis of the nuclear debris Within 24 to 36 hours the phagocytes disappear from the germinal centers leaving only the reticulum and some pigment containing in cells All of the lymphatic tissues decrease in volume and degree of hyperemia and hemorrhages may occur in these tissues The spleen pulp rapidly loses practically all of the lymphocyte cells as well as giant cells and polymorphonuclears

On the basis that vitamin B_1 acts as a co enzyme in the transformation of thymine to thymidine and in view of the possibility that the formation of nucleoprotein might be interfered with by radiation acting on tissue this substance was given by Carter Busch and Strang (*102*)

agents in the tissues. Such changes may be produced by the action of x rays and gamma rays fast and slow neutrons, and beta and gamma particles. The penetrating ability of these rays varies widely and therefore such characteristic must be taken into account when their therapeutic effects are evaluated. For example the alpha rays produce little effect because they do not travel more than a maximum distance of *40 microns*. Nor do the beta rays have much penetrating ability for they are about one half absorbed by 1 millimeter of soft tissue. On the other hand *gamma rays and x rays and fast neutrons have the power of* producing ionization through many centimeters of body tissues. It is obvious from this statement therefore that the gamma rays and the x rays are of the greatest use in clinical radiation therapy.

Variation in Sensitivity of Body Tissues to Radiation.—Of great importance is the striking difference in sensitivity of the tissues of the body to ionizing radiation. According to Warren and Dunlap (*95*) and to Henshaw and Snider (*96*) the following indicates this variation in the body tissues in order of decreasing sensitivity:

1. Lymphocytes
2. Erythroblasts
3. *Germinal epithelium of testes*
4. Myeloblasts
5. Epithelium of intestinal crypts
6. Germinal cells of ovary
7. Basal layer of the skin
8. Connective tissue
9. Bone
10. Liver
11. Pancreas
12. Kidney
13. Nerve
14. Brain
15. Muscle

Of interest also is the great difference in the size of the lethal dose in different animal species. For example according to Prosser (*97*) and to Ellinger (*98*) the guinea pig will succumb to 175 to 250 r whereas a lethal dose in man is about 450 r. The rabbit on the other hand has a lethal dose of 800 r.

***Mechanism of the Effects of Radiation on the Body*.**—*This problem* is being studied intensively and any statements which are made at present must be regarded as purely tentative and subject to revision when additional information is made available. According to Jacobson (*99*) absorption of radiation in cells and fluids of the body is attended by release of energy. This release of energy is considered by many authorities to consist of transient ionization of water molecules followed by the formation of hydrogen peroxide and chemical radicals which in turn inhibit or denature the sensitive enzymes of enzyme systems.

The effect of irradiation is discussed by Warren and Bowers (*100*) who quote a number of investigators and emphasize that the sequence of events which occur when ionizing radiation penetrates a tissue are (1) physical (2) chemical and (3) biological. In other words there is first a physical absorption of the ionizing radiation by the molecules of

150 000 per cubic millimeter or less and there is a "suspected influence" of the x rays if the count is between 170 000 and 150 000 per cubic millimeter Seven of 24 persons engaged in routine roentgen diagnostic work showed a definite decrease in the platelet count and in nine there was an uncertain effect of radiation This observer regards a low platelet count in an otherwise healthy individual engaged in radiologic work as a definite radiation effect He does not consider however that the platelet count should replace other blood examinations but should complement them

The Direct Action of Radiation on the Circulating Blood—When the blood is exposed in vitro to the alpha or gamma rays there is a cessation of the ameboid movements of the neutrophils then degenerative changes occur in the granules and nuclei and finally the cells disintegrate Myelocytes are more susceptible to this damage than the mature neutrophils The earliest effect of gamma rays in mammals in vivo is a lymphocytosis *which may persist if the dose is small but if the dose is moderate or* large it is followed within 48 hours by a leukopenia which affects the lymphocytes more than the other cells Damaged cells may occur in the circulating blood on the third to the fourth day following irradiation On account of the latent period after exposure to radiation it is held by some that injury does not occur directly to the cells in the circulating blood but takes place in the bone marrow Alpha rays likewise cause a severe leukopenia in experimental animals and man but with small doses there may be initial leukocytosis

The effect on the red blood cells may be summarized as follows Both gamma and alpha rays are capable of causing hemolysis in vitro but alpha rays are at least 100 times more effective in producing this than the gamma rays The amount of the radiation is much greater than that required to produce toxic effects in humans It is pointed out by Selling and Osgood (*108*) that anemia is seldom observed in animals who are exposed to heavy dosages of radiation although it is a prominent feature in the majority of cases of human poisoning They explain this on the plausible basis that in animals the leukopenia and thrombopenia develop promptly but the experiment is terminated for one reason or another before there is time for the anemia to develop Furthermore it should be kept in mind that the duration of life of the erythrocytes is thought to be 100 to 120 days whereas that of the white cells and platelets is from four to seven days Hence great injury may be done to the red cell forming tissue and consequently the normal rate of red blood cell formation be diminished Even then as the red blood cells of the circulating blood may not be injured some of them at least may survive as long as 100 days or more As a result an anemia of importance does not develop until a considerable interval has passed

In human cases the dosage has usually been smaller and the duration of exposure longer Hence the survival and period of observation has

in the hope that it might prevent the leukopenia following radiation It was found however, that when this vitamin was administered in single and multiple doses it had no effect on the leukopenia induced in rats by 400 roentgens of 250 kv x rays

The Hemorrhagic Syndrome in Radiation Injury —It was observed by Shouse Warren and Whipple (*101*) that there was a sudden disappearance of the blood platelets from the circulating blood on the seventh to the eighth days after exposure, and a day before the death of the animals They suggest that this thrombocytopenia might be the explanation of the bleeding into the tissues which occurs during the last 24 hours of life A study of the bone marrow indicated that practically all of the megakaryocytes were destroyed by radiation and this gives confirmatory evidence which suggests the origin of the platelets from these cells Furthermore it furnishes some proof that the platelets have a short life cycle of six to seven days in the circulation This observation therefore supports the theory that sudden and extensive bleeding into the tissues may contribute to the death of the animals on the seventh to the eighth days and that the bleeding may be attributed to a destruction of the megakaryocytes in the bone marrow which in turn cause a disappearance of the platelets from the circulating blood

More recently Allen and his associates have attributed the bleeding tendency to a circulating anticoagulant with heparin like qualities which can be neutralized by antiheparin agents (*103 104*) On the other hand Cronkite (*105*) concludes from his observations on goats and swine following atomic bomb exposure that the hemorrhagic syndrome can appear without being associated with a prolonged clotting time or without a detectable heparemia He believes that the most universally observed phenomena in the condition are (1) increased vascular fragility (2) thrombopenia and (3) ulcerations In a more recent publication (*106*) Cronkite and his associates state that the cause of the hemorrhagic syndrome associated with ionizing radiation injury is still poorly understood Following additional experimental studies on dogs exposed to 600 r total body irradiation they conclude that the clotting defect is due to a decrease in the number of circulating platelets While the thrombopenia undoubtedly plays an important if not the most important role in this hemorrhagic syndrome it has not been excluded that the circulation of an anticoagulant may also be of significance in some instances

The Effect of Radiation on the Circulating Blood Platelets —A study has been made by Mossberg (*107*) of the number of platelets in the circulating blood of personnel engaged in roentgen diagnostic work which leads him to the conclusion that in about one third of the cases there is a definite decrease in the platelet count According to this author with the technic employed of counting platelets a definite thrombocytopenia is considered to be present if the count is below

in support of this belief other than misunderstanding and misquotation of a few important papers" They concluded with external ionizing radiations both with acute and chronic application and with internally deposited isotopes that there was no "evidence in the blood forming tissues and peripheral blood of a primary stimulating hematopoiesis" They did observe secondary or compensatory increases in the leukocytes which occur within the first 24 hours after acute exposure to externally originating exposures which they interpret as "reaction to injury mediated through a mobilization rather than a new formation of blood cells" The abortive rise in neutrophils lymphocytes and reticulocytes is likewise probably a result of frank injury

Does Radiation Have an Indirect Effect on Hemopoiesis?—It is established beyond dispute that the aplasia of bone marrow results from direct widespread action of radiation in large doses Lawrence and his associates state (*115*) however that there are some other effects of x rays which are "poorly understood and controversial They are related to possible changes in tissues completely removed from the direct effect of x rays and raise the question of the indirect action of this agent For example it is established that enlarged lymph glands entirely eliminated from any possible effect of direct irradiation may undergo involution when radiation is directed toward remote areas Also the total white blood cell count in leukemia may be greatly reduced when only a small area of marrow is subjected to direct radiation This entire subject is extensively reviewed in a 22 page article with a comprehensible bibliography

In order to produce evidence bearing on this question Lawrence *et al* (*115*) performed 26 cross circulation (carotid to carotid anastomoses) between normal cats and radiated cats In some of the experiments with cross circulation one animal was radiated and the other shielded Detailed examination of the blood was made for a 28-day follow up They concluded that these data did not support the thesis of indirect effects peculiar to radiation A trend toward slightly lowered absolute lymphocyte counts in the untreated animal was observed but they were not significant

THE ACUTE RADIATION SYNDROME

The acute radiation syndrome is the name applied to the manifestations resulting from exposure to ionizing radiation of the entire body or a large part of the body A careful study of this condition has been made by Hempelmann Lisco and Hoffman (*116*) who observed the effects of two accidents at Los Alamos Scientific Laboratory on 10 persons two of whom succumbed The radiations responsible for the pathologic changes were chiefly moderately fast neutrons and hard gamma rays No attempt will be made to give all the details of this most comprehensive

been long enough for the full effect of damage to the erythropoietic to occur. The usual result has been the development of an aplastic anemia characterized by the absence of reticulocytes and nucleated red blood cells but with only slight changes in the appearance of the red blood cells.

It is concluded by Lindemann (*109*) in a most comprehensive study that when erythrocytes are hemolyzed by radiation it can be supposed that the alteration of the permeability of the membrane of the red blood cells which leads to the hemolysis results from its primary denaturation. The most important factor concerned with the hemolysis by x rays is the disintegration of the cellular contents. An acid denaturation and the ray denaturation are analogous. The ray denaturation probably is an indirect effect mediated through the blood plasma.

More recent studies have confirmed the earlier impression that the anemia which develops in man and experimental animals following the external or internal exposure to radiation is due *chiefly* to impaired blood formation in the bone marrow. Certainly in some instances this may be augmented by hemorrhage resulting from a secondary thrombocytopenia which is due to the effects of this agent. It is less clear whether or not an increased rate of hemolysis may also play a role in the production of such an anemia. It is emphasized by Lawrence, Dowdy and Valentine (*110*), however, that the rapid rate of development of an anemia in experimental animals suggests that perhaps hemolysis may be an important mechanism in its production.

The subject of hemolysis due to radiation has been reviewed by Schwartz and his associates (*111, 112*) who believe that it may have a significant effect in producing postradiation anemia. More recently Davis and his associates (*113*) have investigated this subject by studying renal bile fistula dogs subjected to whole body radiation and by observing the effects of radiation of normal human blood in vitro. Although the excretion of bilirubin was increased in these experiments following exposure to roentgen rays, they concluded that the accelerated destruction of mature erythrocytes could neither be proved nor disproved by their observations. Furthermore, the exposure of normal human heparinized blood to x radiation in doses ranging from 10 to 20 000 roentgens failed to throw light on this question. It was their opinion that new experimental approaches must be devised before it can be determined if radiation has a hemolytic effect on mature red blood cells in vivo.

Does Radiation Have a Stimulating Effect on Hematopoietic Tissue?—There has been a difference of opinion for many years concerning the so called stimulating effect of small doses of x ray on the blood forming tissues. The general impression has been, however, that any such stimulus from this source is invariably preceded by a preliminary necrosis of this tissue. The subject has been reviewed by Bloom and Jacobson (*114*). In their opinion little is to be found in the radiologic literature

like substance as suggested by Allen and Jacobson (*119*) Toward the end of the first month the blood platelets fell to a level below 10 000 per cubic millimeter in patients with a severe radiation effect which of course could account for the bleeding at that time

A study has been made by Snell and Neel (*120*) of 924 residents of Hiroshima 20 to 33 months after they had received a sufficient radiation from the atomic bomb explosion to cause scalp epilation The majority of subjects were school children The changes observed were relatively minor The authors conclude that the irradiated subjects appeared for the most part to have made a complete recovery from the depression of the peripheral blood values which may have been assumed to have followed the bombing There remained a slight but significant depression in the red blood cell count the hemoglobin and the hematocrit readings there was a small decrease in the number of lymphocytes and minor elevation of the eosinophils but the total leukocyte count was unchanged It was concluded that the irradiation was to some extent responsible for these small hematologic changes

A study of the effect of total body radiation has been made by Tullis (*121*) who based his conclusions in part on the exposure of swine to total body irradiation from atomic bomb explosions at Bikini in the summer of 1946 He concluded that the lesions produced by exposure to total body ionizing radiations from an atomic bomb explosion are indistinguishable from those produced by exposure of the body to a million volt x irradiation The lesions are those of hemorrhage necrosis and secondary infections He emphasized that the especially sensitive cells of the body are the lymphocytes the myeloblasts germ cells and intestinal epithelium The most primitive hematopoietic stem cells are relatively radioresistant

Summary of the Effects of Radiation on Hematopoiesis—It is emphasized by Lawrence Dowdy and Valentine (*110*) in an excellent résumé of the literature that much confusion concerning the effect of radiation on hematopoiesis may be avoided if the following facts are kept in mind *First* the cells in the circulating blood are relatively immune to the direct effects of radiation except when it is given in tremendous amounts In other words the morphologic constituents of the peripheral blood are highly resistant to the effects of radiation *Second* the peripheral blood picture is strikingly influenced by radiation at any given moment by the length of life of the red blood cells the white blood cells and the platelets As the leukocytes are completely changed in the blood every 10 to 12 hours alterations in these cells occur within a short interval following irradiation As the blood platelets are replaced every four to five days at least in the cat changes in the number of these morphologic elements cannot be expected to occur until after alterations in the leukocytes Finally alterations in the number of erythrocytes of the

study with its appended extensive bibliography but reference will be made in summary only to the hematologic changes They were as follows All patients showed an increase in the total leukocyte count and neutrophil percentage immediately following exposure This disappeared within a few days The initial leukocytosis was succeeded by a leukopenia in three of the 10 patients A lymphopenia occurred in all but three of the 10 patients The cytologic changes occurred only in those patients who received the largest doses of radiation The exception to this statement is the increase in neutral red staining lymphocyte granules which was apparent in almost all patients Examination of sternal marrow indicated that there was rapid destruction of the bone marrow within 2 days and regeneration within three months One fatally injured patient and two survivors showed a moderate fall in the red blood cell count The relative anemias in the survivors were mild and one was of questionable significance Five of the patients showed a fall in blood platelets

The explosion of the atomic bomb at Hiroshima and Nagasaki produced mechanical thermal and ionizing radiation injuries of which the last were the least important in the production of casualties The pathological changes produced by all aspects of the bomb explosion are discussed extensively by Liebow Warren and DeCoursey (*117*) Only the effects of the ionizing radiation on the blood and blood forming organs will be considered here The effects resembled those produced by total body x irradiation of men and animals

The first blood examinations were probably made too late to observe the initial leukocytosis commonly noted within a few hours after exposure The first counts on the day following the bombing indicated a leukopenia which became increasingly severe in the succeeding weeks According to DeCoursey (*118*) one group of cases in the fourth week showed 26 per cent with no white blood cells 16 per cent with none to 2000 per cubic millimeter 33 per cent with 2000 to 4000 and 22 per cent with 4000 to 6000 The platelet counts fell more gradually than the leukocyte counts and the erythrocyte levels fell more gradually than either Although a severe aplastic anemia appeared young forms of the white blood cells and red blood cells were observed within the first 10 days Mature lymphoid cells from the lymph nodes spleen and thymus disappeared by the fourth day Bone marrow tissue was not available until the tenth day but by that time there was almost total loss of hematopoietic tissue In the following three weeks there was persistence of erythroblastic foci but an absence of granulopoietic elements The reticulum cells of the marrow skin and lymph nodes showed a remarkable resistence to ionizing irradiation It is mentioned that the observers at Hiroshima and Nagasaki were puzzled by the appearance of hemorrhages in patients in whom the platelet levels were relatively high It is suggested that perhaps this was due to a heparin

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usually diminished absolutely or relatively, although this may be preceded by an increase. A striking increase has been noted in the number of eosinophils of the circulating blood of radiological workers. The red blood cells are more resistant to the action of the roentgen rays than the white blood cells but once an anemia has occurred the restoration to a normal erythrocyte count is slower. They report that changes in the red blood cells run the gamut from a slight increase in number to a diminution by large doses. 4 It is concluded that the cumulative effect from irradiation cannot be ignored and that such an effect from even minute doses may have momentous consequences to the growth and function of certain cells. The hypothesis of immunization is a hazardous one for there is also evidence that an opposite condition that of anaphylaxis may occur. 5 To the foregoing premises they add the warning that radiologists are not and cannot be shielded from irradiation while pursuing their vocation. They caution that protection can only be relative as the gamma rays of radium and x rays of short length penetrate ordinary barriers appreciably. Hence even with the customary safeguards some degree of scattered and secondary irradiation is inevitable. They review the case histories of six radiologic workers who have died of aplastic anemia beginning with one of the pioneers Dr Tiraboschi an Italian roentgenologist who after 14 years service with little or no means of protection died of a profound essential anemia." They review one case of a well known roentgenologist who developed lymphatic leukemia and report references to several other similar cases observed in roentgenologists. Although exposure to x ray may have no causative relationship to leukemia it is pointed out that it is capable of causing malignant lesions of the skin and may have such an effect on the blood forming organs. The authors refer to Amundsen as stating that the lymphocytes of radiologic workers are regenerated very rapidly and such an overproduction may be regarded as an attempt to compensate for the leukopenia. Hence they quote this author as saying the cases of lymphatic leukocythemia that are reported as having occurred among radiologists may no doubt be interpreted as a lymphocytic regeneration over shooting the mark. The observations of March (*123*) that leukemia occurs nine times as frequently in radiologists as non radiological physicians leaves no doubt in my mind concerning the importance of this agent as an etiologic factor in those exposed to x ray.

As absolute protection is not possible in those working with x ray daily and many roentgenologists become unduly careless in unnecessary exposure in my opinion all x ray workers professional and technical should be compelled to wear some type of holder for a photographic film on their clothing in order to determine the degree of exposure to which they are subjected.

Hematologic Changes Resulting from Exposure to Radium.—In 1926 Martland (*124*) described the case of a 24 year old female dial painter

circulating blood take place only after a much longer period as the life span of these cells is now thought to be 120 days. Furthermore it should be kept in mind that the reduction in the number of red blood cells may be masked by regeneration in the bone marrow which may occur during *the life span of these cells* *Third* it is emphasized by these authors that the difference in the radiosensitivity of the various cells in the circulating blood has an effect on the blood picture produced by radiation It is known for example that the number of lymphocytes in the peripheral blood is reduced earlier and more rapidly than the other morphological elements because their parent cell is known to be more radiosensitive. *Fourth*, the ability of hematopoietic tissue to regenerate is of great importance from the standpoint of the peripheral blood picture It is known that lymphatic tissue has the greatest ability to become active again following injury but also the erythroid myeloid and megakaryocytic *tissues are capable of active regeneration*

In summary it is emphasized by Lawrence Dowdy and Valentine (*110*) that as irradiation probably affects mainly if not entirely, the parent cells of the hematopoietic system the effects to be anticipated in the peripheral blood are importantly affected by the span of life of the circulating cellular elements. The white blood cells show the first changes, and of these alterations in the number of lymphocytes are first to be detected These are followed by a reduction in the number of platelets and the red blood cells

It should be kept in mind that our knowledge concerning the effects of irradiation in general including those on the hematopoietic elements is rapidly expanding Hence it should be reiterated that any opinions expressed at the present moment must necessarily be regarded as tentative ones and subject to revision in the light of additional information which is now being accumulated rapidly

The Occupational Risk of the Radiologists—In a discussion of the occupational hazards of the radiologist with special reference to the blood Carman and Miller (*122*) emphasize among other things the following 1 radium and x rays produce biological effects which are essentially alike, 2 these effects vary according to the amount of radiation and range from stimulation to destruction and 3 cells vary in sensitiveness to irradiation it has been established that the sperm cells the lymphocytes endothelium of the blood and lymph vessels immature cells and cells in the process of mitosis are easily vulnerable These authors consider *that the lymphocytes are the most easily affected* In general they conclude that the circulating lymphocytes show an increased number following small doses and are decreased by large ones They state that among radiological workers there is frequently an increase in lymphocytes either absolute or relative but with severe or long continued exposure a reduction may occur The polymorphonuclear count is

must be in such circumstances some interference with the maturation and delivery of the red blood cells to the peripheral blood stream

In summary it may be said that irradiation in the form of the roentgen rays or radium in sufficient doses will cause the typical clinical picture of aplastic anemia which is indistinguishable from the idiopathic form (*125*) It (*126*) is possible that following exposure to small doses over a long period of time there may develop an anemia with evidences of regeneration in the circulating blood such as nucleated red blood cells According to Selling and Osgood (*127*) this picture resembles that of myelophthisic anemia Furthermore it has long been recognized that granulocytopenia may be produced with a pronounced reduction in the number of white blood cells and evidence of infection as shown by gangrenous and ulcerative lesions of the oral cavity The picture of thrombocytopenic purpura is known to occur following exposure to radiation but this is usually in association with a reduction of the erythrocytes and white blood cells as seen in aplastic anemia The evidence that leukemia may occur in some cases following long exposure to radiation is highly suggestive

The results of a most comprehensive study with an extensive bibliography dealing with the *late effects of internally deposited radioactive material* in man has been published recently by Aub and his associates (*128*) They observed 30 persons containing internally deposited radium alone or in combination with mesothorium who had been exposed at least 25 years ago The fundamental features due to poisoning with these materials were (a) the development of bone destruction often complicated by infection particularly in the case of the jaw bones and (b) neoplasms in or near the bone It was pointed out by these observers that evidence of injury to the blood forming organs which is a conspicuous feature in the acute form of radium poisoning was mild or non existent in these patients The marow of one patient was said to be compatible with that of aplastic anemia but the anemia was mild Leukemia is alleged to be the cause of death in one patient but the observers consider that the patient might have had a leukemoid reaction rather than a true leukemia

The Use of Radioactive Elements in Medicine—Following the discovery of artificial radioactivity by Joliot and Curie (*129*) and the development of the cyclotron by Lawrence (*130*) it became possible to prepare radioactive isotopes of all the stable elements Such elements have become important in medicine in at least two ways first any compound may become labeled for tracer studies by the inclusion of radioactive elements in the molecules and its course and deposition in the body thereby studied For example as cited by Hamilton (*131*) thiamine (vitamin B_1) has been tagged by synthesizing it from radio active sulfur The thiamine thus labeled is then administered to an

who for seven years had pointed brushes with her lips while using luminous paint containing radium. She died after an illness of three years from a progressive anemia with extensive necrosis of the lower and upper maxillae and a terminal broncho pneumonia. Her blood pictures were characterized by a profound anemia in which the color index was usually one plus, by anisocytosis with many macrocytes and by the occurrence of a scant number of nucleated red blood cells, a slight polychromatophilia and occasional basophilia, and a rare megaloblast. The blood platelets were abundant in smears and there was no abnormal bleeding. The van den Bergh reaction in the blood was normal as was the icterus index. The blood pictures were described as "closely resembling addisonian anemia" but there was no evidence of hemolysis. It is of interest to note that the bone marrow at necropsy showed a replacement of the normal adult fat marrow by a red regenerating bone marrow. The marrow of the femurs was dark red throughout and the lesions were more pronounced than that seen in the most characteristic case of pernicious anemia. Histologically the marrow was characterized by an enormous number of nucleated red blood cells, normoblasts and megaloblasts. From this is was concluded that the marrow showed a regenerative change of the megaloblastic type. There were not, however, deposits of hemosiderin of any importance in the spleen, liver, heart or kidneys. It is pointed out by Martland that heretofore the anemias due to radioactivity have been reported as cases of the aplastic variety with little or no evidence of regeneration. He states, however, that the conception was purely a clinical one and not substantiated in his experience. He regards the condition as a regenerative anemia from a morphological standpoint resembling pernicious anemia with the exception that there is no hyperbilirubinemia or siderosis of the organs. The finding of a characteristic picture of aplastic anemia in the circulating blood with a bone marrow which appears to be hyperplastic confirms the statement which is made in the discussion of the classification of the refractory anemias in this section. This is to the effect that the clinical picture of aplastic anemia does not always exist in patients in whom the bone marrow changes are constant. In true idiopathic aplastic anemia the marrow is always hypocellular but with the same clinical picture in association with secondary aplastic anemia it may appear normal or hyperplastic. The only additional point which is of value in differentiating this form of anemia from true aplastic anemia is the history of exposure of the patient to some toxic agent which in this case was radium.

Such a circumstance illustrates that the changes in the circulating blood do not always reflect the alterations in the bone marrow. In such cases even though the bone marrow appears to be hyperplastic it is functionally inefficient in that it does not release the erythrocytes at a normal rate to the circulating blood. Hence it may be said that there

must be in such circumstances some interference with the maturation and delivery of the red blood cells to the peripheral blood stream

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The Use of Radioactive Elements in Medicine—Following the discovery of artificial radioactivity by Joliot and Curie (*129*) and the development of the cyclotron by Lawrence (*130*) it became possible to prepare radioactive isotopes of all the stable elements Such elements have become important in medicine in at least two ways first any compound may become labeled for tracer studies by the inclusion of radioactive elements in the molecules and its course and deposition in the body thereby studied For example as cited by Hamilton (*131*) thiamine (vitamin B_1) has been tagged by synthesizing it from radioactive sulfur The thiamine thus labeled is then administered to an

animal and its fate in the body determined by measuring the distribution of the radioactivity of the radio sulfur in the tissues, body fluids and excreta. A second method is the determination of the emitted rays which can be measured by a Geiger counter tube. For example, if radioactive iodine is administered to a human, it is soon deposited in the thyroid gland. This fact may be demonstrated by placing a Geiger counter over the gland and measuring the intensity of the rays which have been stored selectively in this tissue.

A second use of radioactive elements is a therapeutic agent in the treatment of malignant disease, leukemia and polycythemia. In most instances radioactive phosphorus has been employed for this purpose. This radioactive element (P^{32}) is prepared by subjecting red phosphorus to the action of deuterons in the cyclotron. The radioactive red phosphorus is then converted to disodium acid phosphate (Na_2HOP_4) by suitable chemical means and in this form can be administered to a patient in an aqueous solution either orally or intravenously. The isotope P^{32} *is unstable, having a half life of 14.3 days and disintegrates* according to the following formula $15P^{32} \rightarrow 16S^{32} + B-$ (beta particle). According to Kenney (*132*) the beta particles produced by this disintegration have an average energy of 700,000 volts and can penetrate several meters of air or between 2 and 4 mm of tissue. This particle has the same average energy as the beta particle ejected in soft tissue by 2,000,000 volt x rays. He estimates that a millicurie of radioactive phosphorus, a milligram of radium per se and a millicurie of radon *per se* are identical insofar as the number of atomic disintegrations per second are concerned. They differ greatly, however, in that the radium and radon emit alpha particles and radioactive phosphorus emits only beta particles.

The use of radioactive phosphorus is simply another form of radiation therapy. Its greatest difference is that when administered orally or intravenously it is distributed throughout the entire body, which means that the patient is subjected to systemic irradiation. According to Kenney (*132*) its localization in any tissue is, as far as is known at present, purely a metabolic process and takes place in accordance with the demands of the various tissues for phosphorus. According to this observer, if it should prove to be more effective than the usual radiation therapy, it will be because of this and especially if there is a favorable differential absorption by scattered tumor cells.

It is of especial value in the treatment of such blood diseases as leukemia and polycythemia. The basis for its use in leukemia is that it is known to exert an effect similar to other forms of irradiation which are recognized as beneficial. Furthermore it has been determined that when radioactive phosphorus is injected into animals, bone eventually retains much larger percentages than any other tissue. Hence the ma

terial is deposited in close relation to the bone marrow which is the chief site of the leukemic hyperplasia especially in the myelogenous form of the disease Also studies in leukemic mice have shown that the radio active phosphorus is deposited in leukemic tissue which suggests that this is a method of giving more or less selective irradiation in this disease Furthermore it is known that the beta rays do not have a great penetrating ability and theoretically at least they should be deposited as close as possible to the pathological changes in the body if they are to exert their greatest effectiveness

My own personal experience with the use of radioactive elements in the treatment of leukemia and polycythemia has been limited almost entirely to the administration of radioactive phosphorus and to a lesser extent radioactive strontium They are as effective as other forms of irradiation in the treatment of these two diseases and perhaps further experience will demonstrate that they are even more efficacious They do possess the advantage of being easily administered and in my experience when given in appropriate doses they have not produced untoward reactions

Further discussion of the use of radioactive elements in the treatment of the various forms of leukemia and polycythemia will be found under the sections dealing with the treatment of these diseases

The Untoward Action of Radioactive Elements on the Blood—It is recognized that radioactive phosphorus and undoubtedly other radio active elements may cause important alterations in the bone marrow and consequently lead to significant changes in the morphological elements of the circulating blood A comprehensive review of this action has recently been given by Hempelmann and his associates (*133*) While they acknowledge that radioactive phosphorus is a valuable therapeutic agent in the treatment of polycythemia and the chronic leukemias they emphasize that severe thrombocytopenia leukopenia and a moderate anemia and aplasia of the bone marrow may occur as complications of its use They observed for example that in treating 100 patients with radioactive phosphorus for various hematological disorders 44 developed a thrombocytopenia of less than 100 000 and in 33 of these it was less than 50 000 per cubic millimeter 41 showed a leukopenia of less than 3000 per cubic millimeter and in 36 the red blood cells fell by more than 1 million to a level of under 3 5 millions per cubic millimeter They noted that when more than one of these changes occurred in the same individual the white blood cells usually decreased first the platelets second and the red blood cells third It is of interest to note that the thrombocytopenia and the anemia occurred in some instances weeks after the therapy had been discontinued In three cases of lymphosarcoma and one of Hodgkin s disease apparently an aplasia of the bone marrow was induced by the radioactive material The authors

warn that the blood of patients treated with this form of therapy should be observed at frequent intervals so that the hematological changes can be recognized early and the further administration stopped before irreversible effects on the bone marrow are produced

Aplastic Anemia Following the Administration of Thorotrast (Thorium Dioxide)—A patient is reported by Spier Cluff and Urry (*134*) who developed an aplastic anemia nine years after liver visualization with thorotrast was done to determine the cause of abdominal pain The patient was a 53 year old negress who undoubtedly had an aplastic anemia with a hemoglobin of 3 0 grams a red blood cell count of 1 26 millions per cubic millimeter, a hematocrit of 8 per cent and white blood cell count of 450 to 950 per cubic millimeter The disease terminated fatally and necropsy confirmed the clinical diagnosis

Thorotrast is a 25 per cent colloidal solution of thorium dioxide which emits alpha particles, beta and gamma rays *This element is considered* by some to be a more active disrupter of blood centers than radium (*135*) Tissues obtained at necropsy in the above patient gave evidence of containing radioactive material and thorotrast was thought to be present in the liver spleen and bone marrow sections The authors conclude that in this particular patient the fact that other patients receive a similar quantity of thorotrast and do not develop such an anemia can *only be attributed to differences in individual susceptibility* The literature dealing with the toxicity of radioactive materials is reviewed and a brief resume of the action of thorium in the body is given A comprehensive review of the late effects of internally deposited radioactive materials in man with an extensive bibliography has recently been published by Aub and his associates (*128*)

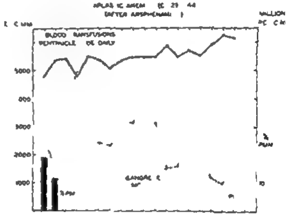
Aplastic Anemia Following the Exposure to Trinitrotoluene—It had been noted that two complications of a serious nature *followed exposure* to trinitrotoluene One was a hepatitis and the other aplastic anemia The literature is reviewed and three fatal cases reported by Eddy (*136*) who states that certain susceptible persons may suffer damage to the bone marrow from this chemical A fatal case of aplastic anemia following exposure to liquid trinitrotoluene for a period of 12 months is reported in a 21 year old female by Davidson Davis and Innes (*137*) Sternal aspiration and examination of the bone marrow at necropsy showed evidences of marked fatty replacement of the hematopoietic tissue An individual predisposition is probably of importance because only rare cases of this condition occur despite the large numbers of workers exposed to the hazard The three fatal cases observed by Eddy (*136*) developed the condition following exposure in environments in which the concentration of the chemical was close to the maximum permissible limit of 1 5 milligram per cubic *millimeter of air*

The outstanding factor in patients with this condition would appear to be exposure to trinitrotoluene dust and fumes for a period of several

weeks to several months According to Hilton and Swanston (*138*) if an employee tolerates the exposure for as long as five or six months he is unlikely to develop any serious toxic manifestations The earliest complaints of those with aplastic anemia are usually those of weakness and ease of fatigue Early in the course of the disease there may be purpuric spots on the skin due to secondary thrombocytopenic purpura Occasionally sore mouth or symptoms of a respiratory disorder may be the only complaints The blood shows the characteristic changes of aplastic anemia namely a pronounced reduction in the red blood cell count the hemoglobin white blood cell count and the platelets

The prognosis in such cases is grave Eddy (*136*) comments that the mortality is high as evidenced by the fact that one half of the first

Fig 45 —Characteristic changes in the blood of aplastic anemia due to injections of arsphenamine In this patient although there was a decrease in the red blood cells the platelets and the leukocytes of the circulating blood the main alteration was in the neutrophils with a *decrease in the total* white blood cell count to less than 1000 per cubic millimeter with 12 per cent neutrophils The patient succumbed to sepsis despite a number of blood transfusions and injections of pentnucleotide This was before the introduction of the sulfonamide drugs and penicillin which might have controlled the condition more satisfactorily than the therapeutic agents which were employed



eight trinitrotoluene fatalities reported in American shell and bomb loading plants during the first 93 000 man years of operations were cases of aplastic anemia Treatment consists in removal of contact with trinitrotoluene careful cleansing of the skin to remove traces of the toxic substance and frequent transfusions with fresh blood This is preferable to bank blood because it is desirable to provide platelets for the patients In bank blood the platelets are frequently agglutinated and probably functionally ineffective

Aplastic Anemia Following the Injection of Organic Preparations of Arsenic —It has been stated by Phelps and Washburn (*139*) that one out of approximately 90 000 patients treated with arsenicals for syphilis develops a depression of the bone marrow which varies in extent The incidence of these complications while not great is more common than

the published reports indicate. This entire subject has been extensively reviewed by Loveman (*140*) and McCarthy and Wilson (*141*).

In almost one half of the hematological disorders following arsphenamine therapy the blood picture is that of an aplastic anemia with a reduction in all of the formed elements of the circulating blood which arise in the bone marrow, namely the red blood cells, the granulocytes and the platelets. Studies show that this may occur following the administration of any form of arsphenamine. The symptoms may occur from one to four months after a course of treatment has been completed but most patients develop subjective evidences of the condition from one to 30 days after the last injection. In most instances however if the blood had been examined repeatedly characteristic changes of the disorder could have been detected earlier.

There is no evidence to indicate that the development of this serious complication is in any way related to the size of the dose or the duration of the treatment. Apparently it is based upon an individual susceptibility and in some instances it may appear after a comparatively short course of treatment in which case it is assumed to be allergic in nature or the untoward symptoms may occur only after prolonged treatment and in such instances the effect of the drug is said to be cumulative. Such an anemia has been reported following the use or arsphenamine neoarsphenamine stovarsol sulfarsphenamine silver arsphenamine bismarsen and mapharsen. According to Moore (*142*) no case of a blood dyscrasia has been observed following the administration of tryparsamide but Kadin (*143*) states that this drug may have been responsible for the changes in the blood in one reported case. In this instance however it was used in combination with other preparations of arsphenamine and hence cannot be incriminated with certainty as an etiologic agent.

Unfortunately, there is no test or information which can be obtained about any given patient which will enable one to predict that such a complication might occur. It is said that when hematological complications develop (*144*) the megakaryocytes are affected first the granulocytes next and erythrocytopoiesis last with purpura a commonly presenting early symptom. In examining the blood of a patient who is receiving any of the arsphenamines for the possibility of damage to the bone marrow it would appear that the earliest anticipated change therefore would be a diminution in the number of platelets then a reduction in the polymorphonuclear cells of the circulating blood and finally a decrease in the number of red blood cells. It is emphasized by Moore and Keidel (*145*) that damage to the bone marrow as indicated by changes in the blood picture is often associated in patients who react to arsenic with a rash of the exfoliative dermatitis group. They urge therefore that in all patients receiving treatment with arsenical preparations an alert outlook should be maintained for the occurrence of itching a

mild macular maculopapular or vesicular rash fever malaise, or any tendency toward purpura Patients complaining of such symptoms may show on blood examination a slight decrease in neutrophils an eosinophilia and an increase in the large mononuclear group which would indicate the necessity for caution in the further treatment of these persons

The clinical picture is indistinguishable from that of acute idiopathic aplastic anemia The course is usually progressively down hill death most frequently occurring in the course of one to four weeks Although the prognosis in all post arsphenamine hematological complications is poor with the exception of purpura it is most unfavorable in aplastic anemia Moore (*142*) in his textbook states that the combined figures from the literature show that the mortality rate in purpura hemorrhagica was zero in thrombocytopenia and granulocytopenia it was 14 2 per cent in granulocytopenia 33 3 per cent and in aplastic anemia 80 5 per cent This last figure compares with that of Wintrobe Stowell and Roll (*146*) who collected from the literature 13 cases of partial or complete recovery

The treatment of this condition has not been satisfactory but in recent years more favorable results have followed the use of BAL (*147 148 149*) The most effective measures of controlling this condition are preventive They should be based upon repeated examinations of blood which of course cannot be done routinely in the large numbers of patients who are given arsphenamine therapy If it were possible to discontinue arsenical therapy at the very earliest sign of significant changes in the red or white blood cells or platelets it is likely that further damage would be averted and more recoveries would occur When the clinical picture of an aplastic anemia has developed in a patient receiving arsphenamine there are four therapeutic measures which should be instituted They are 1 an immediate cessation of all forms of arsenical therapy and never under any circumstances should this form of treatment be resumed 2 the sulfonamides should be given if there is a pronounced reduction in the polymorphonuclear leukocytes in order that infection may be combatted 3 repeated blood transfusions should be administered and 4 BAL may be administered in doses of 3 0 to 4 0 milligrams intramuscularly every three to four hours This may induce some of the undesirable side effects which include lacrimation salivation nausea vomiting hypotension and pulmonary edema They may be prevented by the administration of ephedrine

Aplastic Anemia Following Gold Injections—Since the introduction of gold in the treatment first of tuberculosis and later in patients with rheumatoid arthritis it has been observed that various untoward reactions sometimes followed this form of therapy The early reports beginning in 1932 were largely confined to the French literature According to Wintrobe Stowell and Roll (*146*) who review the subject completely to

the date of their publication (1939) there had been reported to that time 13 cases of aplastic anemia 10 cases of granulocytopenia and seven of purpura hemorrhagica following gold therapy Since it has been recognized that gold is of value in the treatment of rheumatoid arthritis its use has become more widespread and doubtless other cases of each hematological disorder have occurred not all of which have been published With the introduction of new preparations and the recognition that smaller doses are just as effective and perhaps less likely to cause complications the incidence of unfavorable reactions is undoubtedly less frequent than previously indicated by Towle and his associates (*150*) They stated that some constitutional reaction occurred in one of every six patients treated in a group of 451 cases analyzed

The evidence that gold may cause an aplastic anemia is purely circumstantial but it has been generally accepted Attempts to produce changes in the blood of experimental animals with a few possible but unconvincing exceptions have been unsuccessful (*146*) When aplastic anemia does occur in a patient who is being treated with gold the outlook is an ominous one as complete recovery is rare and the patient is likely to succumb to the disease Wintrobe and his associates (*146*) observed a female age 34 who received gold sodium thiosulfate in whom a severe aplastic anemia developed The patient made at least a partial recovery for she was still alive after a period of four years although the blood at the end of that time was not entirely normal as shown by a red blood cell count of 3 6 millions per cubic millimeter and a hemoglobin of 12 6 grams The patient had not received blood transfusions for a period of three years This patient is the third one of their series of a total of 13 cases of aplastic anemia in which death had not occurred at the time of the report and was the second who had made an almost complete recovery

More recently it has been recommended by Marriott and Peters (*147*) that BAL (British anti lewisite 2 3 Dimercaptopropanol) be used in the treatment of arsenic poisoning They regard this also as promising therapy for the control of the hypoplastic anemia due to gold The literature dealing with this subject is reviewed by them Reference is also made to the therapeutic use of folic acid in large doses but they conclude that it is probably not effective A case in point is presented and the suggestion is made when all other therapeutic measures fail that splenectomy may be life saving This procedure is based on the assumption that the blood dyscrasia due to gold may be associated with hypersplenism in some patients It is emphasized that earlier and more frequent splenectomies are not urged in such patients It is their opinion however that when all conservative measures fail splenectomy should be performed

Aplastic Anemia Due to Sulfathiazole—A case of aplastic anemia which followed the administration of sulfathiazole has been reported by

Meyer and Perlmutter (*151*) in 1942 According to these authors this represents the first case associated with the use of this drug which has been reported in the literature The patient had the characteristic picture of aplastic anemia in the blood with a hemoglobin of 5 grams red blood cell count of 1 71 per cubic millimeter white blood cell count of 1600 per cubic millimeter and a complete absence of platelets The patient who had pneumonia was given 1 gram of sulfathiazole every four hours for two days making a total dosage of 12 grams Although it is likely that this patient had aplastic anemia there is no conclusive proof that it was attributable to the sulfathiazole which was given although this is a possibility Strauss (*152*) reports a case of aplastic anemia following the administration of 11 grams of sulfathiazole which was given on account of a low grade infection of the mouth following the extraction of teeth Eight days after the discontinuance of the drug it was found that the hemoglobin was 3 0 grams per hundred cubic centimeters and the red blood cell count 1 360 000 per cubic millimeter The aspirated sternal marrow showed a striking reduction in the number of nucleated red blood cells The patient made a slow but complete recovery

If the sulfonamide drugs are responsible for the production of aplastic anemia it must be an exceedingly rare complication considering the frequency with which these preparations are employed

Aplastic Anemia Due to Atabrine —A study of the effect of atabrine on the blood in a large number of soldiers in the United States Army stationed in the South and Southwest Pacific areas has been made by Custer (*153*) He found that the incidence of aplastic anemia in soldiers taking atabrine was 2 84 cases per 100 000 whereas that in a large control group not taking the drug it ranged between 0 04 and 0 18 per 100 000 His study was based on the statistical evidence just cited and on the material from 57 necropsies on fatal cases of aplastic anemia with symptoms which first became apparent when the patients were in the South or Southwest Pacific areas and almost certainly taking atabrine as a suppressive form of treatment for malaria He states that all had received suppressive doses of atabrine for periods varying from one to 34 months the majority between four and 14 months It appears certain to Custer that atabrine was responsible for the relatively high incidence of aplastic anemia in troops who received this form of therapy From the necropsy findings it was found that the bone marrow was badly depleted of the normal hematopoietic elements often almost completely so and that there was no evidence of extramedullary hematopoiesis One patient who had survived 10 months as a result of 65 blood transfusions had extensive fibrosis of the marrow cavity of all bones examined Apart from the changes in the bone there were the usual extensive hemorrhages involving almost all parts of the body Death resulted in 10 of the 57 cases from cerebral hemorrhage and from massive gastro

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Aplastic Anemia Due to Sulfathiazole.—A case of aplastic anemia which followed the administration of sulfathiazole has been *reported by*

aplastic anemia developed but improved following blood transfusions cortisone and corticotropin gel Even though the red blood cell count and hemoglobin showed distinct improvement the platelets remained at an extremely low level when the patient was last seen

One unexplained feature of the condition is the presence of a fever which may be related in some way with the low granulocyte count and hence a diminished defense against infection There is no contraindication to the use of penicillin in the treatment of this complication as no hemopoietic toxic effect has been observed following the use of this drug

Chloramphenicol has been given to many hundreds of patients with beneficial effects and without causing hematologic complications It must be concluded however that a few patients will develop aplastic anemia following its use and in some the condition will terminate fatally There does not appear to be any method whereby one can anticipate the development of such a serious untoward reaction nor are there any proven safeguards which will be of assistance in the prevention of it The only safe plan to follow therefore is to avoid using the drug except in serious illness such as typhoid fever in which it is undoubtedly the most effective form of therapy available Moreover it should be employed in patients with this disease only when the condition appears to be of serious nature and the risk involved in the use of chloramphenicol is justified

Streptomycin as a Cause of Aplastic Anemia—A fatal case of aplastic anemia following streptomycin therapy has been reported by Womack and Reimer (*178*) and the literature dealing with this subject reviewed In general it may be stated that hematologic complications dealing with a study of the administration of this antibiotic agent in man and animals indicates that they are of a low incidence although occasionally a mild normocytic anemia a leukopenia or a thrombocytopenia may occur I have observed a patient with miliary tuberculosis treated with streptomycin who developed a white blood cell count of 400 per cubic millimeter with a complete absence of neutrophils in the circulating blood It was difficult to determine if the leukopenia resulted from the disease or the medication although in this patient I thought that it was due to the former

The fatal case reported by Womack and Reimer was a 76 year old man who received streptomycin therapy for a laryngeal and pulmonary tuberculosis and succumbed to a fatal aplastic anemia with granulocytopenia and thrombocytopenia Death resulted from gastro intestinal bleeding They stated that this was the third case of such a complication of streptomycin therapy at that time Another case of a 35 year old housewife has been reported by Sacks Bradford and Spurling (*179*) who developed a severe aplastic anemia following streptomycin therapy over a period of four months for pulmonary tuberculosis Recovery followed blood

At the present time I am not aware of untoward hematologic changes following the use of the antibiotic preparations except in those noted above due to chloramphenicol and a few cases attributed to streptomycin (*175, 176*). The association of a hematologic change in a patient who is being treated for any given disease with antibiotic therapy does not necessarily indicate a causal relationship. For example I have observed untreated patients with both typhoid fever and with miliary tuberculosis in whom the leukocyte count had fallen to a few hundred per cubic millimeter. Undoubtedly this was due to the disease, as no antibiotic therapy had been given and no other treatment administered which could have possibly accounted for the leukopenia. In the case of chloramphenicol however sufficient data has accumulated which appears to incriminate this preparation as a definite cause of aplastic anemia. The number who develop this complication is infinitesimal considering the widespread use of this medication. In some patients recovery has followed, in others the condition has terminated fatally usually from cerebral or massive intestinal hemorrhage. In others the condition may become chronic.

In some patients the condition has developed following a relatively short course of the drug whereas in others it has been given intermittently. All ages from infancy to elderly persons have developed the condition. It usually manifests itself initially by the appearance of purpuric spots and bleeding from the mucous membranes most commonly epistaxis. In some instances the initial evidence of the disorder has been the appearance of a definite pallor. Physical examination has usually shown only pallor, petechiae, fever and no enlargement of the spleen, liver or lymph glands. There is usually a normochromic normocytic anemia of moderate or advanced degree and a leukopenia with a white blood cell count often below 2000 per cubic millimeter, with less than 30 per cent granulocytes. A striking feature is the thrombocytopenia with a platelet count which is commonly less than 50 000 per cubic millimeter and not infrequently the platelets are completely absent from the stained blood film. The most striking feature in the bone marrow examination is that the aspirated material may contain only a few nucleated cells chiefly lymphocytes. Furthermore there may be a complete absence of megokarocytes.

The treatment of the condition is unsatisfactory. It consists mainly in the repeated use of blood transfusions until the red blood cell count and hemoglobin percentage are brought to normal. In addition cortisone orally may be given in doses of 75 milligrams every eight hours thereafter. The results of this form of therapy have been only mildly encouraging. The case of a young woman who took chloramphenicol in large doses over a period of seven months for mild acne of the face is reported by Dameshek and Campbell (*177*). A moderately severe

and Bradley (182) state that the reduction in the erythrocytes is frequently accompanied by the presence of a few immature erythrocytes and leukocytes. The blood platelets may be normal or as low as 20 000 per cubic millimeter

OSTEOSCLEROSIS (MYELOSCLEROSIS OR MYELOFIBROSIS)

This condition is non hereditary and usually affects adults The findings in addition to osteosclerosis are splenomegaly hepatomegaly and lymphadenopathy and changes in the peripheral blood The spleen liver and lymph glands show a variable degree of hemopoiesis which is responsible for their enlargement Cases have been described in which the blood picture was as follows 1 myeloid leukemia either with an elevated white blood cell count or of the subleukemic variety 2 with polycythemia 3 lymphoid leukemia or 4 aplastic anemia A complete review of the literature with reference to the different types of blood disorders associated with this condition has been given by Jordon and Scott (*184*) (Reference to the blood picture in association with osteosclerosis which simulates leukemia will be found in the section dealing with leukemia page 859)

Apparently in some cases there may be a pronounced anemia with a reduction in the number of white blood cells and platelets which simulates the blood changes observed in aplastic anemia Such a condition must be rare In such a condition there are usually immature white blood cells in the circulating blood and these findings along with the enlarged liver and spleen should indicate that the condition is *not* one of idiopathic aplastic anemia Furthermore sternal puncture should show evidence of the changes in the marrow and splenic puncture give an indication of myeloid metaplasia in that organ The only treatment for this condition is repeated blood transfusions Certainly splenectomy is contraindicated

Our knowledge concerning the clinical pictures associated with changes in the bone marrow usually aplasia myelofibrosis or bony encroachment on the marrow spaces is incomplete Occasionally a puzzling situation may be encountered in which there is a hyperplastic change in the marrow associated with what appears to be myeloid metaplasia of the spleen

MYELOPHTHISIC ANEMIA

Synonyms —Myelopathic anemia osetosclerotic anemia leukoerythroblastic anemia

Definition —A slowly progressive refractory anemia due to the encroachment in the bone marrow of foreign cells which replace the normal hematopoietic tissue The anemia which results is due to the decreased rate of formation of the red blood cells

transfusions but the circulating blood values did not return to normal for a period of 16 months They suggest that a prolonged course of streptomycin therapy may act on the intestinal flora to produce a folic acid deficiency with subsequent hypoplasia of the bone marrow While such an explanation is possible it lacks convincing proof

OSTEOSCLEROTIC ANEMIA

Osteosclerosis is the term employed to include those rare affections of the skeleton in which the bone marrow is encroached upon or obliterated by a proliferation of connective tissue or deposition of bone Two types of the disease are recognized namely the Albers Schonberg disease in which the so called marble bones occur and osteosclerosis (myelosclerosis) The former is seen usually in children and young adults It is hereditary and is characterized by a heavy deposition of bone of low phosphorus content advancing from the epiphyses In the roentgenogram a homogenous density first compared to marble in 1904 by Albers Schonberg obliterates the bony structure In myelosclerosis there is a diffuse increase in connective tissue or trabeculae in the marrow space leaving the cortex still intact In both conditions there are changes in the bone marrow which result in variable blood pictures one of which is aplastic anemia

Osteopetrosis (Marble Bone Disease, Albers Schonberg Disease) — The disease which was first described by Albers Schonberg in 1904 *(180)* is characterized by an endosteal increase in the thickness and density of the skeletal system and by changes in the hematopoietic system All of the bones of the body may be affected but the alterations are more striking in the vertebrae the pelvic bones the base of the skull the proximal ends of the femurs and distal ends of the tibiae The bones are opaque in the roentgenograms with partial or complete obliteration of the marrow cavities The associated changes in addition to the alterations in the blood are retarded growth pathologic fractures optic atrophy hydrocephalic changes chronic osteomyelitis and imperfect dentition

There is a pronounced reduction in the total amount of bone marrow and this change has been regarded as the primary cause of the myelophthisic anemia The associated enlargement of the spleen liver and lymph nodes were considered to be evidence of compensatory hematopoiesis in extramedullary blood forming organs It has been suggested however *(181)* that osteopetrosis is not a distinct bone disease entity but rather a process affecting the common progenitor of the hematopoietic and osseous systems namely the undifferentiated mesenchyme A review of this condition has been given by McCune and Bradley *(182)*

According to Lamb and Jackson *(183)* the usual peripheral blood picture as recorded in case reports conforms to that of a hypochromic anemia though the terminal stage may simulate aplastic anemia McCune

In some patients with the condition the most significant change in the blood is the presence of immature red blood cells which is out of proportion to the degree of the anemia In one patient with myelogenous leukemia whom I observed although the anemia was not severe and the white blood cell count was not elevated the number of erythroblasts and reticulocytes was so great that the diagnosis of chronic hemolytic jaundice was strongly considered

Diagnosis —Many times the diagnosis of myelophthisic anemia is obvious on account of the presence of unmistakable signs of such conditions as leukemia or Hodgkin's disease but in some instances the nature of the blood disturbance may be obscure Hence when a normochromic normocytic or slightly macrocytic anemia is observed in a patient without obvious cause the possibility that it may be myelophthisic in nature should always be considered Also this variety of anemia should be suspected in patients when there are nucleated red cells or immature white blood cells present in the peripheral blood with little or no anemia

Of great diagnostic assistance is sternal puncture which in many instances will demonstrate the presence of foreign cells It is often exceedingly difficult to differentiate between aplastic anemia and myelophthisic anemia as seen in association with subleukemic leukemia when there is no splenomegaly or lymphadenopathy associated with the latter condition

Treatment and Prognosis —The treatment depends on the underlying cause of the anemia which is usually neoplastic in nature provided one includes lymphoblastoma and leukemia in this group The outlook, therefore in patients with myelophthisic anemia is usually not promising and the survival period is often a matter of months but in some instances it may be for two to three years Not only is the outlook poor because this type of anemia is commonly associated with malignant processes but experience has shown that when such a pathologic condition has advanced so far as to produce an anemia of this type then the duration of life is usually relatively brief

Treatment consists in the possibility of utilizing two therapeutic agents namely (1) the roentgen ray and (2) repeated blood transfusions If there has been bleeding and the anemia is of the hypochromic type then iron in adequate doses will be helpful The antipernicious anemia forms of therapy such as liver or stomach preparations are of no avail except in exceedingly rare cases of monocytic leukemia

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Etiology.—One of the most common causes of this condition is metastases from neoplasms of the breast prostate lungs, and kidney These metastases are most frequently found in the marrow which is active in adult life Other causes are the leukemias Hodgkin's disease and lymphosarcoma in which there is almost always an invasion of the bone marrow and an associated anemia Miliary tuberculosis Albers Schonberg syndrome (marble bones) and the primary xanthomatoses Gaucher's disease Niemann Pick's disease and Hand Schuller Christian's disease may also be responsible for the condition

Symptoms and Signs.—The symptoms are those of a progressive anemia namely weakness pallor dyspnea and palpitation in addition to the manifestations of the underlying condition which is responsible for the anemia In some instances there is said to be deep bone pain with nocturnal exacerbations which Doan (*185*) considers to be pathognomonic but this has not been a prominent feature in the cases I have seen Almost always there is a weight loss with progressive cachexia The gastric secretions usually contain free hydrochloric acid except in patients with carcinoma of the stomach Patients with chronic leukemia may have an elevation in the basal metabolic rates The manifestations peculiar to the various primary causes of such an anemia such as leukemia lymphoblastoma, and others are discussed under the various sections dealing with these conditions

Blood Changes.—The anemia is variable in extent depending on the stage of the primary disease In advanced cases the red blood cell count may be 1 0 *million or less per cubic millimeter and the hemoglobin* in the vicinity of 3 to 4 grams Usually when the patient is first seen the red blood cell count is between 2 5 and 3 0 million per cubic millimeter *and the hemoglobin from 7 to 9 grams* In most instances the color index is high usually 1 0 or slightly less and the saturation index is 0 90 or greater with a mean corpuscular hemoglobin concentration of 30 per cent or more The mean corpuscular volume is generally within normal limits that is between 85 and 95 microns or slightly above normal but rarely does it exceed 110 cubic microns In some cases the anemia may be hypochromic in nature and this is observed more frequently than previously emphasized When this does occur it usually results from bleeding due to malignancy of the gastro intestinal tract or in association with the leukemias or lymphoblastomas

The white blood cells in the circulating blood show various changes depending on the nature of the disease to which the myelophthisic anemia is secondary In leukemia lymphosarcoma and sometimes multiple myeloma abnormal white blood cells may be present The platelet count may be normal or reduced The latter state is usually pronounced in the acute leukemias and is most often associated with a striking tendency to bleed abnormally

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CHAPTER IX

SICKLE CELL ANEMIA

Synonyms.—Sicklocytosis, meniscocytosis, drepanocytic anemia, Herrick's syndrome.

Definition.—A chronic, hereditary and familial hemolytic anemia confined with few exceptions to Negroes or those with an admixture of Negro blood, thought to be due to an intrinsic defect in the erythrocytes and characterized by the appearance of a considerable number of sickle shaped red blood cells in the circulating blood, the symptoms of an anemia, recurrent leg ulcers, cardiovascular manifestations, and acute episodes of abdominal pain, jaundice, nausea and vomiting.

Sickle cell anemia should be distinguished from *sicklemia* or those exhibiting the *sickle cell trait*. Although the red blood cells from such persons when sealed in a wet preparation will assume the sickle shape and other bizzare forms after standing for a number of hours, these individuals have no anemia or other related symptoms attributable to a disturbance of the blood. The exact relationship of this condition to true sickle cell anemia has not been clear in the past. A summary of the present day views concerning it is given on page 467.

History.—It is probable that the earliest references to crescent shaped erythrocytes in the circulating blood were based on the observations of artifacts rather than true sickle cells. In Hayem's book *Blood and its Anatomical Variations* (1) such corpuscles were described and very properly considered to be without clinical significance. Further reference to "half moon corpuscles" was made in 1905 by Sergent and Sergent (2) who found that about 5 per cent of 234 natives of Algiers, composed of Moors, Berbers, Arabs and Negroes, had such changes in their red blood cells. All of these patients had malaria and as the examination of the blood of 265 non malarial patients failed to reveal such alterations they concluded that changes in shape were characteristic of this disease. The same authors also found "demilune" red corpuscles in the blood of European patients with malaria which further stengthened their view that sickle cells occurred characteristically in malaria. It is very doubtful if these observers were dealing in most instances with sickle cell anemia, but as some of their patients were Negroes, it is possible that true sickle cells may have been observed by them occasionally.

In 1904 Dresbach (3) had his attention directed to the blood of a student in his histology class at Ohio State University. The blood at

tracted attention because of the peculiar elliptical shape of the erythrocytes He described them as being distinctly elliptical slightly biconcave non nucleated cells which did not adhere in rouleaux In many of them the biconcavity was barely perceptible" It was estimated that about 90 per cent of these cells did not have the circular outline of normal erythrocytes The average length of the cells was 10 3 microns and the average width was 4 1 microns There were no changes in the hemoglobin content of the blood or the red blood cell or white blood cell counts The student was a healthy mulatto about 22 years of age whose brother had normal red blood cells A short time later in *Science* (*4*), Austin Flint directed attention to these findings and objected to the statement that the subject was healthy In his opinion the changes should be classified under the head of poikilocytosis which is indicative of a pathological condition perhaps, as he mentioned antecedent to purpura hemorrhagica or to pernicious anemia In the following year Dresbach (*5*) supplied additional information which indicated that the subject whose corpuscles had shown such abnormal changes had died of cardiac failure subsequent to an attack of acute inflammatory rheumatism As is often the case the attack was preceded by tonsillitis *which began about three months after my observation had been made* Consequently there was no connection between the condition of the corpuscles and the cause of death

Considerable attention is given to Dresbach's case because it is often cited in the literature either as an example of a person with sickle cells in the blood or one in which human elliptical corpuscles are present Florman and Wintrobe (*6*) state unequivocally that this is the original description of elliptical corpuscles in man rather than sickle cells The evidence indicates that these authors are probably correct in their view Nevertheless the fact that the subject was a mulatto and that he died of cardiac disease at a relatively young age are both strongly suggestive but certainly not conclusive that he might have been suffering from sickle cell anemia The case is of importance only from an historical standpoint for it did not attract widespread interest and probably came to the attention of only a few clinicians when the original description appeared

All agree that the attention of the general medical profession was directed to this disorder by the classical case report of James B Herrick (*7*) which left no uncertainty concerning the clinical features of the disease In this short presentation in which there is not one unnecessary word inserted Herrick delineates the clinical picture in such clear and decisive terms that his description remains a model of clarity and of English exposition I refer my students often to this report as one of the finest examples of medical writing and also one which illustrates how a single case report may constitute a highly important contribution to

the advancement of medicine The case presented was a 20 year old West Indian male who had the typical leg ulcers the cardiovascular manifestations the icteric tint to the eyes and the characteristic anemia A careful description of the erythrocytes is given which includes the statement that "the shape of reds was very irregular but what especially attracted attention was the large number of thin sickle shaped and crescent shaped forms Herrick concludes with the statement No conclusions can be drawn from this case Not even a definite diagnosis can be made the question of diagnosis must remain an open one unless reports of other similar cases with the same peculiar blood picture shall clear up this feature

The case reported by Herrick it is generally agreed is the initial description of the syndrome of sickle cell anemia which directed the attention of the medical profession to the condition His report was followed by those of Washburn in 1911 (8) and of Cook and Meyer (9) in 1915 It was Emmel (*10*) in 1917 who made the first extensive study of the blood of these patients Among other things he noted that when a drop of blood was taken from the patient and placed on a cover slip preparation sealed with Vaseline Petroleum Jelly the number of sickle cells was greatly increased after a short interval Furthermore he observed that when the blood of the patient s father was likewise studied it changed from its normal appearance to one in which many of the cells assumed a sickle shape

It was Mason (*11*) in 1922 who first gave the name Sickle Cell Anemia" to the condition

In 1923 Huck (*12*) made a classic contribution in which he reported 14 cases and drew the following conclusions namely that the condition was a specific disease entity described thus far only in the Negro race that the sickling was due to something inherent in the cells that it is transmitted according to the mendelian law and that attempts to transmit it to animals has thus far been unsuccessful The publications in 1924 of Sydenstricker (*13 14*) served to emphasize the significant changes in the blood and the clinical features but more important than all to bring to the attention of the medical profession the fact that the condition is relatively common in the Negro race for as he says 40 cases have been recognized in our clinic in the past 16 months

Splenectomy as a form of treatment was reported for the first time by Gillespie and Hahn (*15*) in 1927 The first extensive review of the subject was by Steinberg in 1930 (*16*) who gives a complete bibliography to that date

The Sickle Cell Trait and the Hereditary Aspects of the Disorder and Sickle Cell Anemia—The sickle cell trait is a term employed to indicate a condition of the blood characterized by the appearance of sickle shaped erythrocytes after sealed wet preparations have stood for several hours

Stained blood films made in the usual manner do not show such changes In the wet sealed preparations they do not appear for some time, and then in numbers much less than observed in the blood of patients with true sickle cell anemia In some instances it is necessary to employ reducing agents as ascorbic acid according to the method of Daland and Castle (17) to bring out sickling The health of persons with sickle cell trait is apparently unimpaired the blood is without other abnormalities and the previous history of such persons gives no indication that they have at any time suffered from the symptoms and signs of sickle cell anemia

This trait is detectable in the blood of from 8 to 10 per cent of all American Negroes (18) There is usually no difficulty in differentiating between persons with sickle cell anemia and those with the sickle cell trait The criteria used by Neel (18) are of assistance in this respect They are as follows In the sickle cell trait 1 there is no anemia, 2 evidence of increased blood destruction is lacking (normal blood bilirubin) 3 there is no evidence of increased blood regeneration (increased reticulocyte count), 4 the white blood cell count is normal, 5 sickling does not appear on the stained blood film but is observed only after standing in a sealed wet preparation and then the number of cells showing this phenomenon is comparatively few and 6 the patient is asymptomatic

Although the two conditions can usually be easily differentiated, the exact relationship between them in the past has not been clear Increasing evidence is accumulating however to indicate that never does a patient with the sickle cell trait develop active sickle cell anemia nor does a patient with sickle cell anemia change to a latent type with only evidence of the sickle cell trait The statement is made by Wintrobe (19) that no evidence is available to support the claim made by Bauer (20) that in the course of sickle cell anemia the hemolytic process may disappear temporarily leaving only the picture of the trait

Recent studies by Neel (18 21 22) give what is probably the most plausible explanation of the relationship between these two conditions His studies lead him to conclude that the most reasonable explanation of the findings derived from a study of many cases of the trait and true sickle cell disease is as follows The sickling phenomena in patients exhibiting only the trait is produced by a gene in a single dose that is derived from only one parent (heterozygous condition) or as Neel states (18) the sickling phenomenon results from a gene which when represented only once in a person s genetic constitution (heterozygous state) is responsible for the sickle cell trait but when represented twice (homozygous state) is responsible for sickle cell disease At almost the same time and independently a similar hypothesis was advanced by Beet (23) If the hypothesis suggested by Neel and by Beet is correct then the following should occur with the mating of two individuals who

have the sickle cell trait If they become the parents of four offspring one should be entirely normal two should have the sickle cell trait and one should have sickle cell anemia

In studying the manner of inheritance of the sickling phenomenon in 75 families with hematological observations on 465 persons Neel (*18*) observed only two exceptions to the rule that the blood of both parents of a child with true sickle cell disease or that of one parent of a child with the sickle cell trait must sickle He offers as possible explanations of these rare exceptions the following 1 that in certain individuals who are heterozygous for the sickling gene the gene fails to find expression 2 the legal father is not the biological father 3 that which appears to be sickle cell disease is actually due to the interaction of a single gene for the sickling phenomenon with as yet unknown environmental or genetic factors or 4 that the apparently normal parent or parents have actually contributed a sickle cell gene to one or more of the offspring as a result of a mutation occurring at some stage in the formation of the gametes

It seems clear therefore that the sickle cell trait is of little consequence from a clinical standpoint although its hereditary influence may be of significance According to some observers (*24*) the sickle cell trait in the absence of an anemia is of slight clinical importance for the following reasons 1 the trait is compatible with a long life 2 the incidence in hospital patients is no greater than in healthy persons 3 the frequency of leg ulcers and greenish yellow sclerae is as great in Negroes without the trait as those with it 4 hemoglobin determinations of Negro school children show parallel findings in those with and those without the trait and 5 the ratio of the sickle cell trait to sickle cell anemia is estimated as one to 40 but this does not imply that persons with the sickle cell trait eventually develop sickle cell anemia

For the present it must be concluded that the sickle cell trait is commonly encountered in Negroes and that ordinarily it is not associated with symptoms and signs Hence it is probably of minor clinical consequence except in that persons with such a trait may transmit it to their offspring and as suggested by Neel (18) if both parents have the sickle cell trait the offspring may develop true sickle cell anemia

Changes in the Blood in the Sickle Cell Trait —The red blood cells obtained from about 10 per cent of the members of the Negro race when placed in a wet sealed cover slip preparation thereby lowering the oxygen tension of the environment will change their shapes from the normal biconcave disks to elongated forms with sharp ends known as sickle cells Such a process is known as sickling No other pathological changes are known to be associated with this process The blood in persons with this condition shows no abnormalities in the number of erythrocytes the hemoglobin content leukocytes or platelets Such

persons are said to have the sickle cell trait or sicklemia It has been emphasized by Neel (*18*) that the condition may be transmitted to an offspring when one parent has such a trait, and that actual sickle cell anemia may *develop in the offspring* provided both parents have the trait It is recognized that about one person in 40 who has sickling of the erythrocytes has true sickle cell anemia As stated elsewhere however there is no indication that the two conditions may exist in the same person and one state change to the other That is a patient with the trait does not develop sickle cell anemia nor does a patient with sickle cell anemia undergo a change so that only the sickle cell trait is present

It has been demonstrated that a greater reduction of the partial pressure of oxygen is required to produce sickling of the trait cells than is necessary to produce the same change in the erythrocytes of persons with sickle cell anemia Although 30 to 60 per cent of the red blood cells in the venous circulation of patients with sickle cell anemia are of the sickle form less than 1 per cent of those in the venous circulation of persons with the trait have this shape When the erythrocytes from either type of persons are subjected to a sufficient diminution of oxygen tension in vitro however all of the cells of both forms change to the sickle form

The occurrence of Both Sickling and Thalassemia in the same Family—A case is reported by Powell Rodarte and Neel (*25*) of a 38 year old male of Sicilian ancestry who had all of the clinical and hematological findings of sickle cell disease except for the absence of leukocytosis *Since both of his sons had thalassemia minor, it must be concluded* that the father with sickle cell disease also had the thalassemia gene which family studies show must have been inherited from his mother plus a gene for the sickling phenomenon inherited from his father As either one of these genes by itself has only minor effects the occurrence of a severe hemolytic anemia indistinguishable from sickle cell disease in the patient is a noteworthy finding The probability is suggested by *Powell Rodarte and Neel (25) that a situation which results in a person* receiving a sickle cell gene from one parent and a thalassemia gene from the other may account for this condition It is likely according to these authors that a person born of Greek or Italian parents one of whom contributes a sickle cell gene is more likely to receive from the other parent a thalassemia gene than a sickle cell gene

Etiology of Sickle Cell Anemia—*Age and Sex*—The disease probably exists from birth as it is commonly seen in children although it is observed at all ages As it is responsible for a definite decrease in life expectancy it is natural that most of the cases are seen in children or young adults There is no predilection for either *sex* as the condition appears to be equally common in males and females

Incidence—It is pointed out by Neel (*18*) that the improved methods of detecting sickling employed in more recent years may account for

the fact that the studies since 1933 especially indicate a higher per cent of Negroes afflicted with the sickling trait than previously He states that a summary of the findings by other investigators in 5210 Negroes prior to 1933 shows that 6 6 per cent had the sickling trait whereas in 9858 tests since then 10 8 per cent were positive In a study of his own series of 1000 Negro subjects with the more modern tests for sickling (17 26 27 28) positive tests were shown in 9 1 per cent With the newer technics therefore it appears that about 10 per cent of all American Negroes will show the sickling trait a figure somewhat larger than the previously stated incidence

It was found by Tomlinson (29) that when the figures obtained from necropsies native villages and hospital admissions were considered for natives of Central America in 3000 examinations there were 246 instances of sickle cells (8 2 per cent) In 777 routine admissions to Gorgas Hospital Canal Zone of mestizo brown and black patients 56 (7 2 per cent) showed sickled erythrocytes A diagnosis of sickle cell anemia was made in three instances (5 6 per cent) of those showing sickled forms The possibility must be considered that with the use of more modern methods the incidence of sickling in the inhabitants of these areas may have been higher

It is of interest to note that the recent studies of Hodges (30) indicate that the incidence of sickling is less in pure Negroes than in those with small admixtures of white ancestry This same observer did not find that the dilution of the Negro ancestry to such an extent that the person is one half or less Negro will either decrease or increase the incidence of sickling

Although the ratio of persons with the sickle cell trait to sickle cell anemia is given as one which varies from 1 40 to 1 7 according to the opinion of different investigators of the problem the ratio may furnish some idea concerning the actual incidence of sickle cell anemia If the incidence of active sickle cell anemia is taken as 15 per cent (a proportion of one to seven) according to Ogden (31) 135 088 Negroes in this country have the disease and consequently are possibly doomed to complete extermination either in the first or second decade of life This same author estimates that as approximately 7 per cent of all Negroes have the sickling trait there are between 900 000 and 1 000 000 persons with this anomaly in the United States

Race —This type of blood disease is limited almost entirely to persons of the Negro race or those with an admixture of Negro blood There are however at present 13 cases reported in the white race which according to Morrison Samwick and Landsberg (32) have withstood careful scrutiny as to their authenticity These authors add two additional cases occurring in two unrelated white (Italian) families in which it was demonstrated that sickling was present in each case in three generations of each family

It is of interest to note that a majority of cases reported as occurring in members of the white race have been in Greek Italian or Sicilian stock This type of anemia has been observed in other countries but not necessarily in natives of pure stock as in some instances they have been mulattoes and in others the possibility of an admixture of Negro blood has not been excluded Such cases have been reported in Mexicans (*33 34*) in Arabs (*35*) in the natives of Algeria (*36*) in Peru (*37*) in Cuba (*38*) and more recently in Argentina (*39*) and in persons of Spanish decent (*31*) It is insisted however, by Ogden (*31*) that the presence of the sickling trait in a white person is definite proof of admixture of negro blood in the immediate or remote ancestry According to him in no case of the sickling trait in a white person reported up to the present time has the possibility of admixture of negro blood been definitely excluded This observer goes on to state that since it has been demonstrated that a simple dominant non sex linked mendelian character may be transmitted to the bearers descendants for over four centuries and since the sickling trait follows the laws of such transmission it is evident that the admixture of blood may occur as far back as three or four generations and in the case of one of his patients at the time of the Moorish occupation of Spain!

The case of a 19 year old Sicilian girl with sickle cell anemia is reported by Guyton and Heinle (*40*) They review the literature and conclude that 14 well documented cases of sickle cell anemia occurring in white individuals have been recorded Their patient undoubtedly had the disease and a study of five of the nine members of her family were found to have the sickling trait The sickling trait was found to be present in the patient s mother brother a maternal aunt and two maternal uncles Her maternal grandfather an uncle an aunt and cousin were found to be normal The patient s father was not available for study They review the theories of the genetics of the disorder and conclude that transmission as a simple Mendelian dominant is an impossible explanation in many instances They suggest that the homozygous heterozygous theory of Neel is probably correct but that the failure of one or both parents of a sickle cell anemia patient to show sickling is the result of incomplete penetration of the trait producing gene

The first case of sickle cell anemia reported from Egypt is the one observed by Abbasy (*41*) in a 13 year old white girl It was thought that an admixture of Negro blood was reasonably excluded through six ancestral generations The author states that for centuries intermarriages have occurred among the inhabitants of the equatorial border of Egypt and Negroes of the neighboring countries Despite this not a single case of sickle cell anemia had been reported previously This case adds to those already described in subjects of the white race from the Mediterranean area

The Nature of the Anemia.—It has been clearly established that sickle cell anemia is hemolytic in nature and furthermore that the sickle cells in this type of anemia are more rapidly destroyed than normal. This is almost certainly due to an intracorpuscular abnormality. The observations of Singer and his associates (*42*) have shown that trait cells survive for a normal period of 120 days when they are transfused into patients with sickle cell anemia. On the other hand it was observed that red blood cells taken from patients with sickle cell anemia survive for only about one fourth the normal period when transfused into trait carriers. It is clear therefore that the abnormality responsible for the hemolytic anemia in this disorder is inherent in erythrocytes themselves.

It has been considered by Ponder (*43*) that sickling is an expression of an abnormality of the stroma. The hypothesis is advanced however by Singer and his associates (*42*) that if together with this abnormality there exists an additional alteration in the cyto skeleton then the cell structure would become more vulnerable to the wear and tear in the circulation and the life span be shortened.

The cross transfusion experiments of Callender *et al.* (*44*) confirm the observations of Singer and his associates and provide additional proof that the defect in sickle cell anemia is inherent in the red blood cells.

More recent studies have been made by Singer, Motulsky and Wile (*45*) on the mechanism of the crises in sickle cell anemia and its relation to similar episodes in other types of hemolytic crises. From their studies they conclude that a sudden decrease in the red blood cell count in an existing hemolytic syndrome may be due to one of three different mechanisms: 1. the *aplastic type* due solely to a sudden diminution or cessation in the delivery of erythrocytes from the bone marrow to the circulating blood; 2. the *hyperhemolytic type* due to an abrupt increase in the rate of erythrocyte destruction; and 3. the *aplastic hyperhemolytic type* a combination of the decrease in the rate of delivery of red blood cells in association with a greatly increased hemolysis. They report studies on a case of sickle cell anemia in crisis apparently aplastic in nature and emphasize that such a condition should be suspected in a patient with a known hemolytic syndrome of any type when there is an absence of polychromic erythrocytes (reticulocytes) on the blood film.

In studying 26 patients with sickle cell anemia during the acute and chronic phases of the disease increased intravascular hemolysis was observed by Henderson (*46*) as a more or less constant feature of the disease and the resulting anemia and accelerated production of erythrocytes was found during both periods. This observer concluded that sudden massive destruction of the erythrocytes does not appear to explain the symptoms at the time of crisis. The observation is made that variations of in vivo sickling may occur. For example the clinical crisis

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sickling trait is brought in contact with alkali under the same experimental conditions it was found to contain a fraction which is relatively resistant to destruction From their studies and those of others they conclude that at present three different types of hemoglobin can be identified by means of electrophoresis and denaturation with alkali solutions These have been designated as type A (normal adult) type F (fetal) and type S (sickle cell hemoglobin) They advance the hypothesis that the resistant fraction in various hereditary hemolytic syndromes such as sickle cell anemia hereditary spherocytosis Mediterranean anemia and also certain acquired anemias represent a continued production of fetal pigment beyond the physiologic age limit and that the appearance of such an abnormal hemoglobin in the acquired disorders may be *indicative of a reactivation of such a mechanism*

Pathology —One of the important features observed at necropsy in patients with sickle cell anemia is that the capillaries throughout all of the tissues of the body are prominent due to their engorgement with sickle cells This is especially true in the organs of the reticulo endothelial system the kidneys and the lungs It has been suggested (*50*) that this crowding of the capillaries is due to the interlocking of the elongated sickle cells As the maximum sickling occurs in areas in which there is anoxemia it is logical to expect that the distension of the capillaries would be most noticeable in organs where there is the greatest stasis of blood

Another important change in patients with this disease is the tendency toward thrombus formation with infarction This may occur in various organs of the body but is most conspicuous in the lungs spleen and kidneys

Although it is the accepted belief of many pathologists that the abnormal shape of the red blood cells in sickle cell anemia is responsible for the stasis of blood flow in the capillaries resulting in thrombosis and subsequent infarction in the opinion of Kimmelstiel (*51*) this is *not* always the underlying cause of ischemic necrosis in this condition This observer believes that in crisis there is a rapid diminution in the capacity of the erythrocytes to carry oxygen This in association with peripheral vascular spasms may increase tissue anoxia leading to further sickling and the introduction of a vicious cycle These changes may produce ischemic necrosis in inner organs or may be followed by capillary dilatation and stasis at which time the capillaries may become engorged or packed with sickle cells Local ischemia of tissue and capillary walls may *result in organic damage to vessel walls* degenerative changes and thrombosis which results in further infarctions This theory of Kimmelstiel deserves careful consideration At least it affords a plausible explanation of ischemic infarctions which occur in this disease without visible organic changes in the vascular tree

may be associated either with few or many sickle cells in the venous blood although severe sickling is often associated with the crisis but even more pronounced sickling may be observed without clinical symptoms

The State of the Hemoglobin and Its Relation to Sickling.—Studies on the state of the hemoglobin in sickle cell anemia have been made by Perutz and Mitchison (*47*). These were based on the observation that the process of sickling resembled to some extent that of crystallization as a structural change this may be observed to spread throughout the cell from a focus. They found that although the hemoglobin in normal red blood cells and oxygenated sickle cells is not crystalline their experiments indicate that the reduced hemoglobin in sickle cells is in a crystalline state. They believe that with de oxygenation the hemoglobin crystallizes in the red blood cells and that on oxygenation it returns into solution. The change in shape would occur in part because of the habit of the crystals and partly due to loss of water which would be expected to accompany crystallization. The surplus of water which is not inclosed *in the crystals being almost free from protein would have a tendency to* diffuse out of the cells through loss in osmotic pressure and hence cause a collapse of the cell membrane. This hypothesis is offered as a tentative explanation of the sickling process of erythrocytes but as the authors state more work is needed to clear up the problem completely.

Pauling and his associates (*48*) also believe that there is evidence available to indicate that the process of sickling may be intimately connected with the state and nature of the hemoglobin contained in the erythrocytes. It is known that when sickle cell erythrocytes are combined with oxygen or carbon monoxide they have the biconcave disk contour and appear to be entirely normal red blood cells. If the oxygen or carbon monoxide is removed and the hemoglobin thereby transformed to the uncombined state sickling of the cell occurs. This led to the investigations of the state of the hemoglobin by Pauling and his associates who showed that there was considerable difference between the electrophoretic mobilities of hemoglobin derived from red blood cells of normal individuals and that from patients with sickle cell anemia. They concluded that the most plausible hypothesis as to the difference between *the two types of hemoglobin was in the number or kind of ionizable* groups. They also believe that probably the difference is in the globulins rather than the hemes of the two groups. The changes thus detected has led these investigators to believe that a physical and chemical basis has been discovered for the process of sickling in sickle cell anemia and in the sickle cell trait.

Recently Singer Chernoff and Singer (*49*) have discovered that the hemoglobin contained in the red blood cells of patients with sickle cell anemia is alkali resistant. That is when an alkali reagent is brought in contact with normal hemoglobin it is destroyed in one minute. When hemoglobin from patients with sickle cell anemia but not with the

in other organs of the body the essential features of which are con gestion thrombosis and connective tissue replacement (The pathologic changes involving the nervous system are disbursed under the section dealing with the Neurological Disturbance in Sickle Cell Anemia p 481)

Symptoms and Physical Signs —From a clinical standpoint, sickle cell anemia may be divided arbitrarily into several different stages as follows (a) the initial stage which dates from the time of birth until the active manifestations appear (b) the active stage at which time the clinical manifestations of one type or another become apparent (c) the latent stage when the disease is quiescent although of course sickling and probably always some anemia is present (d) the acute phase or stage of crisis characterized by fever jaundice abdominal pain and prostration and (e) the terminal stage when death is imminent

It is possible to recognize several main types of sickle cell anemia depending on the nature of the more important presenting symptoms as follows (a) the febrile type which represents the syndrome of fever of unknown causation (b) the arthritic type (c) the cardiovascular type (d) the type in which lesions of the nervous system predominate and (e) the pneumonic type in which the patient is acutely ill and evidence of consolidation of the lungs appears It is possible this latter condition may result from the presence of multiple emboli in the small pulmonary vessels

Patients in whom the symptoms are restricted entirely to one of the above types are not commonly encountered In most instances during the course of the patient s illness although certain symptoms may be outstanding others representative of several of the varieties are often associated Patients with this disorder may be remarkably free from all complaints for long periods of time despite the persistence of a definite anemia In many however regardless of on sider themselves in good health they will admit that they have some generalized weakness and ea quently a slight icteric tint to the conjunctivae is prese and at variable intervals there are exacerbations of are associated with either a gradual increase in the destruction of red blood cells with a pronounced complaints and a serious degree of prostration

The sudden intensification of symptoms which destruction of erythrocytes is associated with fe nausea and vomiting abdominal pain and p these symptoms when considered with the which is almost constantly present has led to operation The pain may be sharp and stabbing the epigastrium mid abdomen or right or

Evidences of increased blood destruction are the active phagocytosis of erythrocytes by the cells of the reticulo endothelial system jaundice, deposits of hemosiderin in the liver, spleen bone marrow, and a regenerative blood picture

Leg ulcers are commonly present and characteristically appear as a low depressed lesion, oval or round in shape, with a flat grayish granulating base and a smooth slightly elevated margin Microscopically the condition is one of a chronic inflammation which differs from other pathological changes of this kind only in that the capillaries at the periphery of the fibroblastic area are engorged with sickled cells The heart commonly shows hypertrophy and dilatation which usually involves the left ventricle more than the right but in occasional cases in which there are thrombi in the lungs there may be pronounced right sided hypertrophy The endocardium is usually normal in all cases The one exception to this statement in the literature is the case reported by Steinberg (16) in which he states that there was chronic verrucose endocarditis of the mitral and aortic valves with mononuclear infiltration and patchy necrosis of the myocardium

The liver is enlarged and there is a wide distension of the capillaries with sickle cells The Kupffer cells have a greater size than normal and project into the capillary lumens These cells are actively phagocytic and contain many sickled cells and some pigment which may or may not give a positive reaction for iron There is commonly fatty and granular degeneration of the parenchymal cells most frequently involving the central portion of the lobule

The spleen frequently shows a series of progressive characteristic changes from congestive enlargement to fibrotic atrophy A large spleen is most commonly found in early childhood and at this state of the disease it may weigh as much as 240 grams in an infant Fibrotic atrophy usually occurs as the patient becomes older and the organ may entirely disappear or weigh only a few grams The changes in the spleen may be summarized by stating that there is congestion early in the course of the disease, followed by hemorrhage infarction and fibrosis later with siderotic and nodule formation and atrophy

The bone marrow is hyperplastic and practically all of the fat is replaced by actively regenerating cells The flat and cancellous bones of the trunk and the shafts of the tibia and femur are filled with red marrow There is congestion of the capillaries and the tissue spaces with sickled red blood cells Phagocytosis of the red blood cells is not striking In addition to the abnormal hematopoiesis and blood stasis other lesions are found in the bone marrow including thrombosis infarction necrosis hemorrhage granular and crystalline pigment deposits hyalinization fibrous, abnormal calcification and new bone formation According to Diggs and his collaborators (50) these lesions are similar to those found

in other organs of the body the essential features of which are congestion thrombosis and connective tissue replacement (The pathologic changes involving the nervous system are discussed under the section dealing with the Neurological Disturbance in Sickle Cell Anemia p 481)

Symptoms and Physical Signs —From a clinical standpoint sickle cell anemia may be divided arbitrarily into several different stages as follows (a) the initial stage which dates from the time of birth until the active manifestations appear (b) the active stage at which time the clinical manifestations of one type or another become apparent (c) the latent stage when the disease is quiescent although of course sickling and probably always some anemia is present (d) the acute phase or stage of crisis characterized by fever jaundice abdominal pain and prostration and (e) the terminal stage when death is imminent

It is possible to recognize several main types of sickle cell anemia depending on the nature of the more important presenting symptoms as follows (a) the febrile type which represents the syndrome of fever of unknown causation (b) the arthritic type (c) the cardiovascular type (d) the type in which lesions of the nervous system predominate and (e) the pneumonic type in which the patient is acutely ill and evidence of consolidation of the lungs appears It is possible this latter condition may result from the presence of multiple emboli in the small pulmonary vessels

Patients in whom the symptoms are restricted entirely to one of the above types are not commonly encountered In most instances during the course of the patient s illness although certain symptoms may be outstanding others representative of several of the varieties are often associated Patients with this disorder may be remarkably free from all complaints for long periods of time despite the persistence of a definite anemia In many however regardless of the fact that they consider themselves in good health they will admit on close questioning that they have some generalized weakness and ease of fatigue Frequently a slight icteric tint to the conjunctivae is present Spontaneously and at variable intervals there are exacerbations of the disease which are associated with either a gradual increase in the anemia or a rapid destruction of red blood cells with a pronounced accentuation of all complaints and a serious degree of prostration

The sudden intensification of symptoms which occurs with a rapid destruction of erythrocytes is associated with fever increased icterus nausea and vomiting abdominal pain and prostration In some instances these symptoms when considered with the increased leukocyte count which is almost constantly present has led to an ill advised abdominal operation The pain may be sharp and stabbing in nature and referred to the epigastrium mid abdomen or right or left sides of the abdomen

When such crises occur, there is often a striking decrease in the hemoglobin and red blood cell count of the peripheral blood (A further discussion of this aspect of the condition is given on p 480)

The patients are usually under developed and poorly nourished The physical findings depend on whether the patient is in a crisis or in the more chronic phase of the disease Ordinarily there are several findings of importance on physical examination One is a slight icteric tint to the conjunctivae another is the presence of leg ulcers and a third is cardiac hypertrophy The spleen may be enlarged especially in the earlier stages of the disease but it is never greatly increased in size and when the condition is advanced it is not palpable In fact, there is evidence which indicates that as the disease progresses there is atrophy of this organ which may reach a point at which it practically disappears and cannot be found even at operation

Chronic Leg Ulcers—Either chronic leg ulcers or healed scars are present in three out of every four adults with the disease but they are uncommon in young children In most instances the ulcers appear at about the ages of 14 to 15 years The common site is the lower third of the leg on the anterior surface or about the ankle They are frequently large and may be multiple and bilateral A typical ulcer appears as a round or oval shallow depressed erosion with a flat gray granulating base and a smooth slightly elevated margin As a rule only a small amount of exudate is present In general it is said that they have a smooth punched out appearance which suggests a syphilitic ulcer for which they are often mistaken In some patients there remains only a round or oval well healed scar with clean cut edges

It is known that chronic leg ulcers may occur in association with different types of hemolytic anemia and have been observed in Banti s syndrome idiopathic thrombocytopenic purpura Gaucher s disease pernicious anemia and chronic hemolytic polycythemia (52) Two patients with leg ulcers one with hemolytic anemia and the other with pancytopenia (secondary hypersplenism) are reported by Gendel (52) He suggests that the association of leg ulcers with various diseases of the blood may be related in some unknown manner to either splenomegaly or hyperfunction of the spleen

The Heart—It is recognized that the heart is commonly enlarged in this condition and in some instances the cardiac symptoms are so prominent as to dominate the clinical picture In one of my patients the diagnosis of rheumatic heart disease had been made on the basis of the complaints of dyspnea and palpitation cardiac hypertrophy and a history of generalized aches and pains which were a part of the sickle cell anemia syndrome but misinterpreted as evidence of rheumatic fever

If the anemia is of long standing there is almost always considerable cardiac hypertrophy which is apparent during life as well as at necropsy

Often there is a loud systolic murmur which may be due to a combination of a relative insufficiency associated with the cardiac hypertrophy and the factors which are responsible for a so-called "hemic murmur" As the heart is enlarged and often contracting vigorously there may be a pseudo-thrill which is systolic in time This is likely to be more apparent in children in whom the chest wall is thin In some instances there may be a diastolic murmur associated It has been emphasized by King and Janeway (53) that electrocardiographic changes similar to those found in rheumatic fever such as prolongation of the P R interval may be present in patients with sickle cell anemia The electrocardiographic changes in this disorder have also been reviewed by Winsor and Burch (54)

A summary of our knowledge of the heart changes in this disease has been given by Klinefelter (55) Recently Brugsch and Gill (56) have drawn attention to the fact that cardiovascular disease joint pain and fever may occur in Negroes with sickle cell anemia residing in the Northern States and may be confused with acute rheumatic fever The most logical explanation of the cardiac hypertrophy is the persistent anemia which of course imposes an added amount of work on the heart over a long period of time In this respect the cardiac enlargement is on the same basis as in erythroblastic anemia (thalassemia)

In a study of 62 cases of sickle cell anemia Higgins (57) records that the initial diagnosis was rheumatic heart disease in 22 congenital heart disease in three arteriosclerotic heart disease in one and hypertensive heart disease in one Although certainly it is possible that any one of these conditions may co-exist with the cardiac condition associated with sickle cell anemia it is probable that in almost all if not all the heart manifestations were entirely due to the sickle cell anemia This same author summarizes the cardiac symptoms and signs in the 62 cases of sickle cell anemia as follows presence of cardiac murmurs 45 presence of cardiac enlargement by percussion or x ray 38 enlarged liver 27 presence of congestive failure three presence of electrocardiographic changes 17 in 21 cases

It is stated by Higgins (57) that coronary thrombosis apparently does not occur in this condition but angina pectoris is "common" and may be relieved by correcting the anemia The case of a 22 year-old Negro with sickle cell anemia in crisis which simulated closely the clinical picture of coronary thrombosis is reported by Jones Wetzel and Black (58) In this patient the electrocardiographic evidence was compatible with coronary thrombosis These changes were quickly but only partially reversed after the hemolytic crisis subsided Marked myocardial damage was anticipated at necropsy but only simple hypertrophy and moderate interstitial edema was observed These pathological findings are often observed in a variety of types of severe anemia

The Acute Abdominal Manifestations of Sickle Cell Anemia.—A certain proportion of the patients develop crises in which there may be abdominal pain and tenderness, fever, leukocytosis, sometimes jaundice and variable degrees of shock. In not a few instances patients with such symptoms have been admitted to the surgical divisions of a hospital and an abdominal operation performed. Needless to state, when acute abdominal complaints occur in any Negro, the possibility of sickle cell *disease should be kept in mind and the blood examined for sickling*. The abdominal conditions most commonly simulated are acute appendicitis, intestinal obstruction, intussusception, perforation of a hollow viscus or acute cholecystitis. The following list of incorrect diagnoses of a surgical nature is reported as made in a series of patients with sickle cell anemia by Patterson, Wilson and Diggs (*59*): acute appendicitis six, possible intestinal obstruction four, renal colic three, pelvic inflammatory disease three, possible acute surgical abdomen two, acute cholecystitis one, mass in right lower quadrant, one, possible ruptured appendix one, ruptured intervertebral disk one, intussusception one, liver abscess one, and undiagnosed abdominal pain one.

The cause of abdominal symptoms in patients with sickle cell anemia is obscure. Numerous theories have been advanced, among them being arterial thrombosis (*60*), vertebral changes with pressure on the nerve roots (*61*), an intra-abdominal visceral disorder as a splenitis (*62*), splenic hemorrhage (*63*) and splenic thrombosis (*64*).

The causes of abdominal pain are reviewed by Crastnopol and Stewart (*65*). They emphasize that the principal cause may be mesenteric and retroperitoneal lymphadenitis and lymphadenopathy; other secondary causes may be thrombotic episodes, co-existent hepatitis and hepatosis, splenitis and perihepatitis. These authors concur with others that all Negroes deserve a study of a wet sealed blood preparation for sickling of the red blood cells when there is any suggestion of an abdominal complaint requiring surgical treatment.

Skeletal Changes in Sickle Cell Anemia.—The roentgenograms in a majority of patients with sickle cell anemia show no significant changes in size, shape or density of the bones; in some, alterations of moderate degree are present, and in a small number, usually adolescents or adults, the abnormalities are striking. A detailed discussion of the roentgen ray changes in bone will be found immediately following this section.

The changes in the bones are regarded as due primarily to alterations in the bone marrow (*50*) in which two factors are active but operating in opposite directions, namely, one, the hyperplastic marrow increases in volume at the expense of bone, and the other, the sclerosing factor which in part may replace the marrow and substitute in its place osteoid tissue or new bone. When the hyperplastic marrow does have an effect, it is observed in those bones which normally are engaged in blood cell forma-

tion such as the skull and the cancellous bones of the trunk. The process in these bones is predominantly one of osteosclerosis. In the long bones in which hematopoiesis does not occur sclerosis is the characteristic abnormality. These two opposing factors of marrow expanding and marrow contracting may lead to gross anatomical changes in the bones if the patient survives a sufficient period of time.

A recent review of the literature dealing with this aspect of sickle cell anemia is given by Hamberg (66). This author concludes that sickle cell anemia may be suspected from the x ray findings but it cannot be diagnosed definitely from this type of evidence alone. He emphasizes that in the older patients the symptoms of bone and joint disease may cause the patient to consult a physician rather than symptoms referable to the anemia. It is his conclusion that the bone changes are due to a combination of bone marrow hyperplasia and repeated infarction.

The Roentgen Ray Findings in Sickle Cell Anemia.—A definite diagnosis of sickle cell anemia from the roentgen ray findings alone can be made in only rare instances. It is often possible however to detect roentgenological evidence which points strongly to that diagnosis. A comprehensive review of this subject and an outline of the findings in this type of anemia is given by Carroll and Evans (67). They state that the following roentgenological changes may be observed in this type of anemia:

A. *Long Bones*
 1. Thinning of the cortex and widening of the medullary cavity
 2. Prominent trabeculation
 3. Thickening of the cortex with narrowing of the medullary cavity
 4. Periosteal elevation
 5. Bizarre bone architecture with replacement fibrosis

B. *Skull*
 1. Osteoperosis and widening of the diploe
 2. Thickened skull usually in localized areas
 3. Perpendicular striation

C. *Pelvis and Spine*
 1. Osteoperosis with accentuated trabeculation
 2. Biconcave vertebrae

D. *Chest*
 1. Enlarged heart
 2. Osteoporosis and accentuated trabeculation of the ribs
 3. Pulmonary edema
 4. Pulmonary thrombosis

Neurologic Disturbances in Sickle Cell Anemia.—Neurologic disturbances are not rare and in some instances cause serious manifestations

such as convulsions meningeal signs aphasia paralyses coma and death The lesions in the brain in such disorders are primarily vascular as indicated by the most common findings at necropsy which are dilatation of the blood vessels and congestion with sickled erythrocytes This occurs most commonly in the vessels of the cortical gray matter and those within the subarachnoid spaces over the hemispheres Additional changes of the greatest importance and those responsible for the more serious clinical manifestations are multiple thromboses These may involve the small vessels of the subarachnoid areas over the cortex and also be present in the large dural sinuses and the cortical branches of the cerebral artery especially the middle cerebral branch The vascular lesions consist of changes in the intima with fresh and organized thrombi which lead to a narrowing of the lumina of the vessels and a resultant impaired blood supply Consequently the gray matter and to a less extent the white matter are involved in an acute and chronic degenerative change with resultant widespread clinical manifestations The brain changes are similar to those observed in the spleen and bone marrow in which there is stasis thrombosis infarction parenchymal degeneration and fibrotic atrophy

The basis of the pathologic lesions in this condition is primarily stasis with related subsequent changes Factors which increase the stasis are the elongated sickle cells the increased number of leukocytes nucleated red blood cells macrocytes and in some cases the effect of obliterative changes in the arterioles of the lungs and myocardial failure With the presence of anoxemia there is an increase in the sickling which is responsible for vasodilatation and stasis and hence in turn also increases the anoxemia The combination of stasis and anoxemia can readily lead to endothelial injury and subsequent thrombus formation According to this view the arterial changes are interpreted as being due to capillary and venous thrombosis with chronic stasis and a diminishing volume of blood flow to various parts of the brain Another view (68) is that endothelial and proliferative changes observed in the arteries in sickle cell anemia are the primary lesions and that the other phenomena are secondary

The main clinical manifestations as stated by Hughes *et al* (69) from a study of their own cases and a consideration of those in the literature are as follows the most common are drowsiness stupor and coma hemiplegia and aphasia Those which are fairly common are headache convulsions stiffness of the neck pain in the back and neck abdominal pain irritability facial weakness aching extremities and stiffness of the legs Those which have been observed but are relatively uncommon are stiffness of the back nystagmus pupillary changes vomiting transitory blindness ptosis generalized rigidity dysphagia paresthesia of the extremities diplopia left homonymous hemianopsia paralysis of the third and fourth cranial nerves weakness of the left side of the tongue

anesthesia and analgesia of the right side of the body nasal regurgitation marked salivation and delirium

The spinal fluid may or may not show changes of importance In some instances even with extensive clinical findings the spinal fluid may be entirely normal in all respects In others it may be bloody or yellow in appearance the pressure may be increased and the protein and cell count above normal The clinical manifestations are exceedingly variable as indicated by the list just given This is to be expected from the wide spread nature of the lesions which are known to exist in the cerebral cortex and meninges The prognosis in such conditions must necessarily be poor and no effective therapy is known

A case is reported by Thompson Wagner and MacLeod (*70*) in a 20 year old colored male in whom the clinical picture was first that of an atypical spontaneous arachnoid hemorrhage and later that of an acute diffuse hemorrhagic encephalitis with a fatal termination The major pathologic lesions were sickle cell disease and cortical vein thrombosis with intense passive congestion of cortical veins and capillaries Subsequently there was apparently rupture or erythrocytic diapedesis which *produced diffuse confluent destructive cortical hemorrhages* The blood examination during life showed a hemoglobin of 15 grams a red blood cell count of 4 95 millions per cubic millimeter white blood cell count of 13 800 per cubic millimeter with a normal differential formula Tests for sickling were not done The case is reported as one of sickle cell disease with cerebral manifestations in the absence of an anemia This is a most unusual situation as sickle cell disease with cerebral manifestations is usually associated with an anemia and sickling should be apparent in the blood smear The lesson to be stressed is that in the presence of cerebral disease in a member of the Negro race the possibility of sickle cell disease should be kept in mind and repeated and careful blood studies done with the newer technics in order to determine the presence or absence of sickle cell anemia

Sickle Cell Disease and Pregnancy —Experience indicates that sickle cell disease represents a definite hazard during pregnancy to both the mother and child *It was found by Beacham and Beacham (71) that* the incidence of pregnancy in association with sickle cell disease in Negro patients in New Orleans was not great as it occurred in only about 6 per 10 000 deliveries On the other hand the complication was a serious one when it did occur as one out of every five mothers died as an obstetrical patient and only approximately two thirds of the gestations recorded both in the literature and in Charity Hospital have yielded living offspring The association of the two conditions therefore represents a serious threat to the health of the mother and the fetus This may be attributed to the clinical course of the associated disorders among the most important being the low tolerance to infection of the mother

On account of the seriousness of the blood disorder as a complication of pregnancy, it should always be kept in mind as a possibility in Negro patients. In all pregnant members of this race, therefore, sickling preparations should be made when there is an anemia, jaundice, severe illness or a history of the disease. If the patient is found to have the sickling phenomenon, *a complete hematological survey should be made*. It should be emphasized, however, that in those who have only the *sickling trait* in which the sickled red blood cells are not apparent on an ordinary blood film and the blood in all other respects is normal, there is no added risk imposed by pregnancy. For example, it was found by Switzer and Fouche (72) that the sickle cell trait was present in 14.2 per cent of 500 gravid colored women in the Charleston, South Carolina area. Of the 71 women with the sickle cell trait, anemia was present in only one. It was the conclusion of these observers that sicklemia does not interfere with normal pregnancy and delivery. It seems important, therefore, in all pregnant Negro women who have the sickling phenomenon in the blood to differentiate between the *sickle cell trait* and *true sickle cell disease* with its associated anemia. In the former condition apparently pregnancy does not result in any added hazard to the mother or the child; the latter disorder, however, adds a definite risk to both fetal and maternal mortality and morbidity.

It is the opinion of Beacham and Beacham (71) that patients with sickle cell anemia are entitled to optimum obstetrical care. They do not believe that the disease per se is an indication for the interruption of pregnancy, but that the associated conditions may favor such a procedure. The patients should be hospitalized early and treatment of the complications be instituted promptly. Blood transfusions should be administered to all such patients with a significant anemia, severe infection or impending shock. When liberal use of penicillin, sulfonamides and blood transfusions is made along with early hospitalization, it is the belief of Anderson and Busby (73) that a more optimistic prognosis is justified in such patients. Their figures justify this statement. For example, no deaths occurred in the 11 mothers they observed over a 20 year period, and the fetal mortality was 15.2 per cent, which is considerably less than previous estimates. In their opinion therapeutic abortion and sterilization is seldom indicated in patients with sickle cell anemia associated with pregnancy. On the other hand, it is pointed out by Beacham and Beacham (71), in making such a decision it should be kept in mind that the disease certainly has no beneficial effects on the anemia and that most of the patients in the sickle cell category do not live long enough to rear their children.

Priapism and Sickle Cell Anemia.—Priapism is a rare finding but is occasionally observed in patients with sickle cell anemia. According to Getzoff (39) in the five year period ending November 1, 1941, 57,455 male Negroes were admitted to the Charity Hospital of Louisiana at

New Orleans Of this number 65 males were discharged with the diagnosis of sickle cell anemia During this same interval 11 Negroes were recorded as having priapism and three of these patients had associated sickle cell anemia It is thought that a possible explanation of this finding may be in the venous congestion of the organ with lowering of the oxygen tension and pH of the blood which favors stasis and further sickling of the red blood cells Such changes may be responsible for thrombosis formation A thrombus thus formed may act to occlude some of the vascular channels concerned with the venous return from the penis Consequently further stasis occurs a vicious cycle is thus established and priapism ultimately results

Fundus Oculi—It is common to have striking dilatation and tortuosity of the veins of the fundus and to a lesser extent the arteries Edema of the nerve head is not seen nor is there compression at the point of crossing of the veins and arteries Furthermore there is no evidence of unevenness of caliber of the vessels In some instances there may be thickening and tortuosity of the superficial temporary vessels

Blood in Sickle Cell Anemia—When the blood of a patient with sickle cell anemia is placed in a sealed wet preparation and examined immediately it will be noticed that a majority of the cells are round or oval but that some are irregularly shaped and others are elongated and have sharp pointed ends After such a preparation has been standing for two to six hours the rate of change is at the maximum and within 12 to 24 hours the metamorphosis is complete These alterations can be accelerated by placing a rubber band around the end of the finger thereby rendering the blood more anoxemic before the sealed preparation is made

The cells vary in outline and such terms as sickle cell fish fin oat and crescent shapes have been employed to describe their appearance The most characteristic cell associated with the disorder which is rarely seen in any other condition is elongated pointed at each end and curved in the middle and one well filled with hemoglobin Such cells may be as long as 50 microns and as narrow as 1 to 2 microns Usually however they are from 10 to 20 microns in length and vary in diameter from 2 to 4 microns in greatest width

The number of sickle cells in stained films is highly variable in different patients In some there may not be a sufficient number present on some examinations to warrant a diagnosis of this type of anemia The number of cells are fairly constant from month to month in certain patients while in others there is a wide variation Diggs and Bibb (74) state that in a majority of patients they were present in numbers between 5 and 20 per cent Apparently there is no correlation between the percentage and the severity of the anemia

The size of the erythrocytes may be exceedingly difficult to determine in the presence of many sickle cells in the stained films In cases where

they do not exceed 5 per cent, it has been found that the average diameter is somewhat increased, usually varying between 8 and 9 microns. The average in one group of cases was 8.17 microns (*74*).

Electron micrographs of sickle cells according to the new technic of Rebuck, Woods and Monaghan (*75*) confirm the findings of Diggs and Bibb (*74*) as to the structural detail of these cells.

The Price-Jones measurements resemble to a certain extent those seen in the blood of patients with pernicious anemia, as there is a wide base to the curve indicating pronounced anisocytosis and the peak is to the right of normal at about 8.5 microns.

Recent studies reported by Murphy and Shapiro (*76*) suggest that sickling is a property inherent in the susceptible erythrocyte. Their studies indicate that as the cells age the tendency to sickle becomes more pronounced. They conclude that sickling is unrelated to alterations in the electrolyte ionic balance but that the level of the available potassium in the cell may play a significant role in the phenomenon. (A further discussion of the sickling phenomenon will be found on p. 474 under the heading of Etiology.)

It has been noted by Tomlinson and Jacob (*77*) that erythrocytes capable of assuming sickle shapes will do so when re-suspended either in normal saline, their original plasma or serum or in other compatible plasma or serum *provided* they have not been washed more than five times in normal saline. It is their opinion that long washings remove some substance which is necessary for sickling or for the exchange of carbon dioxide and oxygen which makes sickling possible. They make the suggestion that carbonic anhydrase is the substance involved although they have no direct proof of this.

The number of reticulocytes is increased, as they frequently make up 25 per cent of the erythrocytes and average about 15 per cent. Nucleated red blood cells are almost always present, as are cells with diffuse and punctate basophilia. Howell-Jolly bodies and Cabot's rings may be observed. In some instances it has been noted that the sickled cells contain a nucleus.

Volume measurements of the erythrocytes indicate that the anemia is of the normochromic normocytic type with a slight tendency toward a microcytosis as the anemia becomes severe. The average measurements reported by Diggs and Bibb (*74*) in 44 cases were mean corpuscular volume 90 cubic microns, mean corpuscular hemoglobin 29 micromicrograms and mean corpuscular hemoglobin concentration 32 per cent.

Fragility tests of the erythrocytes as determined by the resistance of the cells to hypotonic solutions of sodium chloride show that they have an *increased* resistance. In 15 cases (*74*) it was found that hemolysis began with an average concentration of 0.34 and was complete at 0.11 per cent as compared to 0.42 and 0.32 for the controls. In some instances it has been found that the red blood cells will remain intact even in dis-

tilled water. It has been observed, however (74), that the erythrocytes in patients with sickle cell anemia are less resistant to mechanical shaking than are those from normal persons.

When well developed symptoms are present, there is usually an anemia of moderate degree, although it may be severe (1.0 to 1.5 millions per cubic millimeter). The hemoglobin is reduced proportionately, and hence the color index is usually in the vicinity of 1.0. During the periods of latent sickle cell anemia, when symptoms are mild, the red blood cell count is usually between 3.0 and 3.5 millions per cubic millimeter.

The white blood cells are almost constantly increased in sickle cell anemia, and in periods of crises, when there is rapid destruction of the erythrocytes, the count may be as high as 20,000 to 30,000 per cubic millimeter. This increase is due mainly to mature neutrophils, but there may be occasional young granulocytes and myelocytes. The eosinophils may be present in greater numbers. In some instances there is also an increase in the monocytes, and if a careful search is made, these cells may be observed with engulfed erythrocytes.

The platelets are usually moderately increased, the count sometimes being as high as 500,000 per cubic millimeter. There is no change in the bleeding or clotting time.

Especially during periods of crises there is a hyperbilirubinemia of variable degree, usually being between 15 and 25 units as measured by the icterus index, but it may be greater than this. The van den Bergh reaction is indirect and is commonly between 1 and 2 milligrams per 100 cc. of blood. The urine shows an increase in urobilinogen and urobilin.

Electrophoretic studies of the plasma and serum proteins in patients with sickle cell anemia show certain non-specific changes according to the report of Fenichel, Watson, and Eirich (78). They found in a study of 15 patients with the disease that hypoalbuminemia was present in 13, elevated gamma globulin in 12, elevated beta globulin in three, and reversal of the A/G ratio in 12 cases. There was an increase of the fibrinogen in eight of the 10 cases for which it was tested. It was their conclusion that these changes were not specific but due to tissue breakdown caused by the sickling process in various organs, particularly the liver.

There are no characteristic changes in the gastric secretion as determined by gastric analysis.

The sedimentation rate is usually below normal. This has been explained by some on the basis that rouleaux formation is prevented by the shape of the sickle cells. A comprehensive study of the various factors which affect the sedimentation rate in patients with sickle cell anemia has been made by Winsor and Burch (79), which provides another basis for changes in the sedimentation rate. They found that in six of 10

patients with the disease that the sedimentation rate was slow when compared with the packed cell volumes The patients with the most severe anemia had the slowest rates They concluded from various experimental studies however, that it was not the anemia itself which produces the retardation but some other factor which changes concomitantly with the decrease in erythrocytes Their studies indicate that the sedimentation rate of blood saturated with oxygen was invariably accelerated, and the sedimentation rate of blood saturated with carbon dioxide was always retarded The retardation may be so great that severely anemic blood will not settle more than 2 to 3 millimeters in four to five days Furthermore evidence indicated that it is carbon dioxide per se and not the change it produces in the pH that so significantly slows the rate of sedimentation of the erythrocytes They observed that the sedimentation can usually be correlated with the type of rouleau formation being rapid when rouleau is normal and somewhat slow when it is abnormal and very slow when it is absent It is their opinion however that other factors than rouleau formation affect the sedimentation rate Their observations show that the sedimentation rates of patients with sickle cell anemia may be slowed or accelerated by alternate saturation with carbon dioxide and oxygen that is, the sedimentation rates are reversible and vary considerably Normal blood is affected only slightly by these gases It should be kept in mind that a tourniquet when kept on the arm for 10 minutes retards the sedimentation rate in patients with this type of anemia

The Phenomenon of Sickling and Methods of Demonstrating Sickling of the Erythrocytes —The phenomenon of sickling is closely related to the concentration of reduced hemoglobin in the red blood cells In almost all tests for sickling it is necessary to produce reduced hemoglobin This may be accomplished by the removal of oxygen from the erythrocytes by means of a vacuum pump (80) or by the displacement of oxygen in the blood sample with such gases as hydrogen nitrous oxide carbon dioxide or nitrogen (15 28 81) Prompt reversion to the normal discoidal form will result from exposure of the red blood cells to oxygen or carbon monoxide As pointed out by Daland and Castle (17), a second principle is to cause a reduction in the oxygen tension of the blood by permitting it to be consumed metabolically This is accomplished in vivo by placing a rubber band around the end of the finger for several minutes before the sample of blood is removed or in vitro by placing the blood in a sealed wet cover slip preparation so the oxygen tension is reduced probably as a result of consumption of the oxygen by the leukocytes To achieve this same end it has been proposed by Daland and Castle (17) that the reduction of the hemoglobin be accomplished by a chemical agent namely ascorbic acid The technics of the various methods of inducing sickling have been summarized by Neel (18) In addition to the simple method of preparing a

simple wet sealed preparation and observing it at once at the end of six hours and again at 24 hours a satisfactory method is the one devised by Daland and Castle employing ascorbic acid (*17*)

Recently a rapid carbon dioxide test for sickling has been devised by Hanno and Margolies (82) It is based on the principle that carbon dioxide when introduced into a flask creates a relatively poor oxygen environment In addition the acid effect of the carbonic acid formed by the reaction of the gas with the blood decreases the affinity of the hemoglobin for oxygen They regard the test as simple dependable and rapid

A study has been made by Mickler and Diggs (83) of the value of the sodium bisulfite methods as compared to the "moist stasis" method for the detection of the sickle cell trait They conclude that the former has several advantages among them being that the diagnosis can be made within 15 minutes

Bone Marrow—The characteristic change is a hyperplastic marrow with 50 to 75 per cent of all cells being nucleated blood cells The predominating type is the normoblast Megaloblasts as seen in the blood of patients with pernicious anemia are not present There may be some immaturity of the myeloid leukocytes and an increase in eosinophils The number of megakaryocytes is greater than normal

The bone marrow is typical of the type seen in hemolytic anemia and the only finding to distinguish it from other hemolytic anemia is the presence of sickle cells

Diagnosis—The diagnosis can be made with a considerable degree of certainty The occurrence of a hemolytic type of anemia which is normocytic and normochromic in character in a Negro or in a person with an admixture of Negro blood or in rare instances in an individual of Italian Sicilian or Greek stock should at once bring to mind this variety of anemia as a diagnostic possibility If in the stained films there are the characteristic sickle crescent or oat shaped forms the diagnosis is almost certain Additional confirmatory findings are the presence of a leukocytosis nucleated red blood cells in the circulating blood and an increase in the reticulocytes

The history alone is quite distinctive for there is usually a statement that the patient has had the manifestations of a chronic anemia for some time and that recurrent febrile attacks with severe pains in the body have occurred usually in the joints bones or abdomen Important physical findings are jaundice cardiac enlargement hepatomegaly and leg ulcers In the early stages the spleen is enlarged but as the disease progresses this organ becomes atrophic In many instances there are characteristic roentgenological changes in the skull and long bones Sickle cell anemia is not so often confused with other types of anemia as it is with acute febrile diseases such as rheumatic fever acute

arthritis, osteomyelitis, appendicitis catarrhal jaundice meningitis and typhoid fever

Treatment and Prognosis —There are no specific measures for the treatment of this form of anemia Liver extract ventriculin and iron alone and in various combinations are without effect It is claimed by some that blood transfusions do not seem to be as effective as they are in other types of anemia as the transfused blood appears to be destroyed with considerable rapidity In some instances this procedure is followed by extremely severe and sometimes dangerous reactions

Splenectomy has been recommended in younger patients in whom there is splenomegaly but the results attained in my opinion have not justified the operation The first splenectomy in this condition was reported by Hahn and Gillespie in 1927 (*15*) They stated that great improvement followed this procedure in the single patient on whom it was performed Subsequent observations, however have not borne out this early optimistic report Recently however Shotton Crockett and Leavell (*84*) have reviewed the entire subject of splenectomy in this disorder and conclude that in cases of sickle cell anemia showing various indications of hypersplenism and excessive hemolysis splenectomy may be a rational procedure This recommendation should be accepted with caution however as the most which could be anticipated from such an operation is a temporary remission the value of which must be balanced against the risk and discomfort of a major operation

The only therapy of value is the regulation of the patient s life so that the activities are commensurate with the degree of anemia steps taken to insure an adequate diet and the use of symptomatic measures Travis Winsor (*85*) of the School of Medicine of Tulane University has observed that normal red blood cells when given as a citrated transfusion survive in the blood of a patient with sickle cell anemia for an interval of about 90 days He advocates therefore the administration of a blood transfusion four times yearly in order to combat the anemia Such a recommendation appears to be a logical one unless untoward reactions occur from this form of therapy He also suggests that oxygen inhalations be given for patients in crises who have acute pain or in those with pulmonary complications

The sickle cell trait appears to be harmless except that it can be transmitted to the offspring but if both parents have the trait sickle cell anemia may be present in some of the children

Sickle cell anemia must be regarded as a serious disease for several reasons Many patients do not survive after the first decade of life and rarely live longer than the third decade Death may be due to intercurrent infections of which pulmonary tuberculosis is a prominent one Apparently some succumb to the crises of the disease Others may die of uremia as a result of extensive renal involvement or of serious

cerebrovascular changes. Abortions and still births are common but in some instances a normal child may be born

Even though a patient may survive for a considerable period of years the disease is a serious handicap on account of the chronic anemia the leg ulcers the cardiac complaints and recurrent crises

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CHAPTER X

OVALOCYTOSIS

Synonyms.—Elliptocytosis, elliptical cell trait.

Definition.—This may be defined as a hereditary condition characterized by the occurrence in the circulating blood of large numbers of elliptical erythrocytes usually with normal cell size and hemoglobin content, in which the longitudinal axis is at least 1.5 times greater than the short axis and as a rule, not associated with symptoms.

The carrier state has been defined arbitrarily by Wyandt, Bancroft, and Winslup (1) as characterized by the presence of at least 25 per cent of elliptical erythrocytes in the circulating blood of a healthy person; persons with 40 per cent or more are regarded by these authors as true cases of elliptocytosis. In my opinion there does not appear to be any other difference between the carrier and the true state except that in the latter a small per cent of the patients have a hemolytic anemia associated. In other words, the carrier state in this condition resembles that in hereditary spherocytosis except that the responsible gene for ovalocytosis much less frequently attains the level of clinical significance.

This condition should not be confused with various other blood disorders in which increased numbers of ovalocytes may be present. This occurs in thalassemia, sickle cell anemia, pernicious anemia and the sex linked hypochromic microcytic anemia described by Cooley (2) and by Rundles and Falls (3). In such conditions the number of ovalocytes is usually relatively small and the symptoms and signs of the condition place patients with these conditions definitely in a different category. At present it is generally conceded that a person with ovalocytosis is usually healthy but in a small per cent there may be a hemolytic anemia with associated symptoms.

History.—Probably the earliest case of this condition noted in the literature was the famous one of the mulatto medical student in whom a chance observation revealed that 90 per cent of his cells were elliptic rather than round. This example was reported by Dresbach (4) in 1904. Although he contended that the subject was healthy and that the blood alteration in the erythrocytes was not indicative of a pathological condition, this was contested by Flint (5). This case is usually cited in the literature as the initial one observed, but it is possible, as Ewald wrote to Dresbach, that a similar case had been observed in Königsberg, Germany, 20 or 30 years before. Also Lambrecht (1938) reported that

in 1860 Goltz had observed a woman with the condition in Konigsberg and it is possible that both may have been referring to the same person In 1914, Bishop (6) reported two more cases a brother and sister, both of whom were perfectly healthy in all respects

Since that time many of the cases have been reported In 1941 Wyandt Bancroft and Winship (1) gave a most comprehensive review of the literature and cited 246 definite cases of elliptocytosis occurring in 64 families To this group they added 86 new cases of their own occurring in three large German families

Although Bishop (6) and Huck and Bigalow (7) and others mentioned that more than one case occurred in a family it was the comprehensive study of Hunter and Adams (8) of three generations of a Dutch American family which definitely established the hereditary nature of the condition Additional observations were made later on other members of the same family by Hunter (9) and by van den Bergh (10)

One of the most comprehensive articles in the literature dealing with the subject is that of Leitner (11)

Etiology —*Age and Sex*—It is usually stated that the condition may occur at any age and is present equally in both sexes In the largest group reported in the literature (1) however, the trait was more frequent in males than females

Incidence —The incidence in the general population is usually given as between 0 04 and 3 per cent with the lower figure probably being nearer the correct one according to Miller and Lucas (12) Four instances of the anomaly were discovered in 10 000 examinations by McCarty (13)

There is no question but what elliptical cells in small numbers occur in the blood of a considerable number of normal persons but in such small numbers that the finding does not warrant classifying them as having the elliptical cell trait In the study of Wyandt Bancroft and Winship (1) of 450 students and nurses it was found that 58 per cent had 1 per cent or less of elliptical cells 37 per cent had 2 to 5 per cent 4 per cent had 5 to 10 per cent and 1 per cent had 10 to 15 per cent During the four years in which their study was in progress only two additional cases were found in the course of approximately 7000 examinations It should be noted however that in some subjects they found as many as 10 per cent of the cells to be elliptic

They state that those individuals with 40 per cent or more elliptical erythrocytes in the circulating blood should be regarded arbitrarily as true cases of elliptocytosis those with 25 to 40 per cent they designate as carriers In my opinion there does not appear to be any difference between the carrier state and a true case except the per cent of elliptical cells in the circulating blood since in both instances the condition is generally conceded to occur in normal persons

Heredity —In 1932 Cheney (14) after studying the condition in three generations concluded that ovalocytosis is transmitted as a true men

deli in dominant characteristic. This has been amply confirmed. One family is reported (*1*) in which both parents and one child had the condition and one child did not; this proves that it could not be a recessive characteristic (*1*). It is said by Bernhardt (*15*) that in only one instance has ovalocytosis been observed in which it was known that the red blood cells of both parents were normal in shape. This could be explained on the same basis as isolated cases of hereditary spherocytosis, namely, the changes in the blood of parents may be so minimal as to be overlooked, or even the most refined tests may be inadequate to determine the hematological abnormality in some persons. The possibility must also be considered that the condition may have skipped one generation (*16*). A Negro male has been observed by Neel (*17*) in whom ovalocytosis was present but neither of the parents exhibited the disorder, although both had the sickle cell trait. The father's red blood cells showed moderate microcytosis with slight increase in anisocytosis and poikilocytosis, and these findings may have an etiological relationship to the blood changes in the son.

Marriage between two individuals with ovalocytosis has been reported by Wyandt, Bancroft and Winship (*1*). Of the five children from this marriage, two died in infancy, two were normal, and one had striking ovalocytosis with a hemoglobin of 9.8 grams of hemoglobin, a red blood cell count of 4,200,000 per cubic millimeter. The indirect van den Bergh was positive, the red blood cell fragility was strikingly increased, and the reticulocyte count was high. Spherocytosis as well as splenomegaly and a distinct icteric tint to the skin were present, and a history suggestive of hemolytic crises was obtainable. As Neel states (*17*), "It is tempting to regard this extreme picture as resulting from homozygosity for the gene in question." In other words, it may be possible that such a condition is the result of inheritance of characteristics from two genes, one from the father and one from the mother, which Neel believes is responsible for sickle cell anemia and thalassemia major.

Association of Ovalocytosis with Additional Changes in the Number of Erythrocytes and Their Hemoglobin Content.—Undoubtedly, a great majority of the patients with true ovalocytosis have otherwise a perfectly normal peripheral blood in all respects and, furthermore, the patients are free from all symptoms referable to the condition. A small number, probably 10 to 12 per cent, have a slight associated anemia of the hemolytic type with symptoms of a mild to moderate intensity associated with it. In addition, there is a third group to which reference will be made later, in whom the red blood cell count is actually increased, although there are no symptoms due to this condition.

It was noted by Penfold and Lipscomb (*18*) in their study of between 350 and 400 cases from the literature that about 12 per cent had an anemia. The possibility arises, however, in my opinion, that cases other than true elliptocytosis may have been included in this study. It is

known that true elliptical erythrocytes may be present in patients with pernicious anemia sex linked microcytic hypochromic anemia and other anemias Such conditions however are not examples of true ovalocytosis Undoubtedly cases of hemolytic anemia do occur in association with typical ovalocytosis and probably it is the only type of anemia which is directly associated with this hereditary blood disorder As Cooley says (2) if anemia is ever associated with elliptocytosis of the dominant hereditary type it is most commonly a condition distinguished from congenital hemolytic anemia only by the cell anomaly" This observer stated in 1942 (19) that in 246 cases of ovalocytosis in the literature 35 or 15 per cent were anemic On the other hand Wyandt Bancroft, and Winship (1) in a study of 86 persons with ovalocytosis in three interrelated families found no evidence of anemia although they did not give the detailed hematological findings Cases in which there has been a definite associated anemia are reported by Lambrecht (20) Bertelsen (21) and Mason (22) A patient with elliptical erythrocytes was observed by van den Bergh (23) who stated that all of the manifestations of hemolytic anemia were present except increased fragility of the red blood cells Following splenectomy the jaundice in this patient receded but the elliptical erythrocytes persisted In 1948 I saw a female 21 years of age who complained of ease of fatigue A great majority of her erythrocytes were elliptical and a moderate hemolytic anemia was present The red blood cell count was 3 0 millions per cubic millimeter the hemoglobin 10 3 grams per 100 cc or 66 per cent the hematocrit 33 per cent the mean corpuscular volume 110 cubic microns the white blood cell count 14 150 per cubic millimeter the blood bilirubin 1 5 milligrams per 100 cc of plasma and the reticulocytes 10 per cent The patient appeared to be in good health with the exception of a questionable slight icteric tint to the skin the spleen was palpable about two finger breadths below the left costal margin The patient s father was healthy but was said to have a slight yellowish color when tired His red blood cell count and hemoglobin of the peripheral blood were within normal limits but there was definite but slight anisocytosis and poikilocytosis and a moderate number of elliptical forms The reticulocytes were 5 per cent in the peripheral blood The blood of the patient s mother was normal The patient had a splenectomy and three months later the red blood cell count was 4 5 million per cubic millimeter the hemoglobin 13 2 grams (85%) the white blood cells 14 700 per cubic millimeter, and the reticulocytes less than 1 per cent The oval forms still persisted in approximately the same number as prior to the splenectomy but the patient was completely free from the symptoms which she had previously experienced namely weakness and fatigue

One can only speculate about the cause of the anemia in patients with ovalocytosis As stated by Penfold and Lipscomb (18) although they have brought forth evidence indicating that elliptocytosis can and does

cause hemolytic anemia the nature of the mechanism producing the anemia is not known and they can only postulate that the elliptical cells are destroyed because of their age or due to some essential structure anomaly

In summary therefore all evidence indicates that in a small number perhaps between 10 and 12 per cent of the patients with ovalocytosis there is likely to be a slight to moderate anemia of the hemolytic type This is indicated by the presence of a normocytic normochromic anemia an increased reticulocyte count in the circulating blood a palpable spleen an increased blood bilirubin and a return of the blood to normal following splenectomy In van den Berghs patient (23) in whom splenectomy was performed the jaundice receded but the elliptocytosis persisted as was true in the patient whom I observed

It is of interest to note that the patients with elliptocytosis may have a polycythemia This was first noted by Stephens and Tatelbaum (24) In a study of 15 members of a family with elliptocytosis they reported that the average red blood cell count in the eight affected members was 6 47 million per cubic millimeter and the average of the seven unaffected members 5 13 million per cubic millimeter In one of the persons with an elliptocytosis the erythrocyte count was 7 27 million per cubic millimeter the hematocrit reading 46 per cent the mean corpuscular volume 64 cubic microns the mean corpuscular hemoglobin 21 micromicrograms and the mean corpuscular hemoglobin concentration 33 1 per cent The authors comment that in each of the affected individuals there was a definite increase in the red blood cell count but a decrease in the mean corpuscular volume and mean corpuscular hemoglobin In general they observed that the number of red blood cells was inversely proportional to the mean cell volume and the hemoglobin content

The presence of a red blood cell count which is increased above normal in the individuals has also been noted by Penfold and Lipscomb (18) who suggest the following theory the elliptical erythrocytes may have increased susceptibility to destruction by the reticulo-endothelial system as is observed in spherocytosis In most instances the destruction is not great and compensation is accomplished by a slight increase in erythropoiesis If the cell destruction is greater however than the increased red blood cell formation a hemolytic anemia would result On the other hand if the increased production surpasses normal and exceeds the increased cells destruction a polycythemia may result This theory although plausible lacks substantiating proof

The Nature and Mechanism of Production of the Elliptical Cells — According to Stephens and Tatelbaum (24) the blood of eight healthy subjects with ovalocytosis showed from 20 to 56 per cent of all their cells to be elliptical in shape although in the literature the number which have been observed varied from 10 to 90 per cent In no instance has

100 per cent elliptical cells been noted These observers state that in wet preparations the oval and elongated cells are apparently biconcave ellipsoids Persons with definite elliptocytosis have a red blood cell count which may tend to be high in some instances and according to Stephens and Tatelbaum (24) there is a decrease in the mean corpuscular volume and the mean corpuscular hemoglobin

It was noted by Strauss and Daland (25) that when washed oval red blood cells were suspended in normal saline 2 5 per cent sodium citrate solution in their own serum in their own plasma there was no detectable change in shape Nor did they observe a change in the form of normal washed erythrocytes when suspended in serum obtained from subjects with ovalocytosis Furthermore when fresh wet sealed preparations of blood from 10 patients with ovalocytosis was incubated at 37 degrees for 24 to 72 hours there was no increase in the number of oval cells similar to that observed in sickle cells when blood is studied under these conditions from patients with the sickle cell trait On the other hand Wagner (26) in studying the blood from a healthy adult Negro whose erythrocytes were distinctly elliptical found that these abnormally shaped cells rounded up in sealed preparations within 24 hours Furthermore they could be made to assume their original oval shape when plasma from the subject was added to the preparation According to this observer this atypical behavior perhaps represents the reaction of a subject with an intermediate type of ovalocytosis

Studies by Daland and Strauss and others (25) have not demonstrated in any of the patients that there is an alteration in resistance to hypotonic saline solutions

There is some evidence to indicate that the elliptical shape is assumed by the erythrocyte in the older cells In support of this is the observation by Schartum Hansen (27) that none of the nucleated erythrocytes in sections from the bone marrow are elliptical and the observation by Strauss and Daland (25) that the younger erythrocytes in the circulating blood the reticulocytes are not commonly oval and if so only to a slight degree

It is reported by Wyandt Bancroft and Winship (1) that sternal puncture was done in two cases of ovalocytosis In each case approximately 80 per cent of the non nucleated red blood cells were elliptic although all of the nucleated erythrocytes and a majority of the reticulocytes were round or nearly so No evidence of increased erythropoiesis was found The fact that the majority of the reticulocytes and the normoblasts in the bone marrow were round suggests as has previously been noted that the elliptic form is assumed after the reticulocyte stage

It is of interest to note that in studying the blood of an infant between the ages of two and one half months and four months it was observed by Helz and Menten (28) that there was a progressive increase in the per

centage of elliptical cells up to the fourth month when the condition apparently became stabilized

Two studies have been made in an attempt to determine the length of life span of elliptical erythrocytes and the evidence reported is in conflict In 1938 Vischer (29) following transfusion experiments reported that the transfused elliptical red blood cells had a shorter life span of 12 to 13 days as compared to the 30 day interval which he considered to be normal at that time More recently Trinick (30) using the Ashby differential agglutination technic reported that transfused elliptical cells from a donor in which 90 per cent of the cells were oval survived in a patient with bleeding peptic ulcer for 100 to 110 days a period which is now considered to be normal

Clinical Manifestations —Ordinarily as ovalocytosis is defined there are no symptoms or signs associated with the condition It is usually detected as a result of a routine blood examination or during the course of a study of some family thought to have the elliptical trait In possibly 10 per cent there may be a mild hemolytic anemia with associated pallor a slight icteric tint and a palpable spleen The only symptoms are slight ease of fatigue and weakness

Treatment —As symptoms are usually absent in almost all patients with elliptocytosis there is no treatment indicated If however such a patient develops a hemolytic anemia with an increased number of reticulocytes in the peripheral blood an increase in the blood bilirubin and a palpable spleen then the possibility of a splenectomy should be considered Such a procedure is likely to give complete relief If the operation is not done the condition may persist throughout life

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CHAPTER XI

HEREDITARY LEPTOCYTOSIS

Mediterranean Anemia

Synonyms.—Cooley's anemia, thalassemia, erythroblastic anemia, Mediterranean anemia, disease or fever, target cell anemia, familial microcytic anemia, hereditary or familial poikilocytosis.

Definition.—The severe form of this anemia (thalassemia major) may *be defined as a rare hereditary, chronic, progressive, pronounced hypochromic microcytic anemia* of obscure origin, confined almost exclusively to peoples of the Mediterranean area or their descendants, characterized by erythroblastosis, decreased fragility of the erythrocytes, splenomegaly, hyperplastic changes in the bone marrow with increase in the medullary bone spaces, a resistance to all forms of therapy, and usually a fatal termination in infancy or childhood.

Thalassemia minor is a carrier state of thalassemia major which occurs mainly in well nourished persons almost entirely from Mediterranean stock. It is characterized by hypochromic microcytic erythrocytes commonly oval in shape or appearing as "target cells," with increased resistance *to hypotonic saline solutions*, the *hemoglobin values* are usually below the normal range with a disproportionately high red blood cell count; sometimes there is an associated moderate leukocytosis, reticulocytosis, elevated icterus index, and splenomegaly.

History.—*Patients with this type of anemia were originally* described by the late Thomas B. Cooley, the well known pediatrician of Detroit. In 1925 he with Dr. Pearl Lee (1) presented the abstracts of five cases before the meeting of the American Pediatric Society. At this time he stated that such cases had been known previously as Von Jaksch's disease or pseudo leukemic anemia. The anemia, splenomegaly, the discoloration of the skin, the absence of bile from the urine and the many nucleated red blood cells in the circulating blood were accurately described. The mongoloid features and the roentgen ray alterations were also noted. In a later report (2) he emphasized its occurrence in the Mediterranean races, the reticulocytosis, the increase in the icterus index, the increased resistance *of the erythrocytes*, and suggested that splenectomy might retard the course of the disease. In this publication he ventured the idea that although hemolysis is a constant feature the condition should not be considered as primarily a hemolytic disorder.

Excellent summaries of our knowledge of the disease and reviews of the literature have been written by Baty, Blackfan, and Diamond *(3)* Parsons and Hawksley *(4)*, Yaguda *(5)*, Flynn *(6)* and Silvestroni *(7)*

In 1936 Whipple and Bradford *(8)* made a comprehensive pathological study of the condition and tested many therapeutic measures without avail They considered that the disease might be due to some racial inherited defect possibly a deficiency state The name Thalassemia" derived from the name great sea was suggested by them to replace the original designation of erythroblastic anemia used by Cooley

The terms thalassemia major and thalassemia minor were suggested by Valentine and Neel *(9)*

The possibility that the severe disease was due to homozygosity for an inherited factor which when heterozygous produces the mild disorder was first suggested by Caminopetros in 1938 and the theory developed further by Gatto *(10)* Dameshek *(11)* Chini *(12)* Silverstroni and Bianco *(13 14)* and Valentine and Neel (9, 15)

Etiology —Age —The earliest evidences of the disease appear at any time during the first decade of life usually during the first two years The average age when the initial manifestations appear is about 16 months The symptoms at the onset are usually of slight severity and medical attention often is not sought until the child is three years of age or older Undoubtedly mild cases are not recognized until adult life or they may be entirely overlooked The disorder rescribed as target cell anemia by Dameshek *(16)* and the mild type of Mediterranean anemia in Italian adolescents observed by Wintrobe and his collaborators *(17)* is now designated as thalassemia minor and is thought to result from a heterozygous state of a gene

Sex —The malady occurs with equal frequency in both sexes

Racial Incidence —Since the earliest descriptions of the disease a distinct racial distribution has been apparent The condition occurs most commonly in Italians especially Sicilians Greeks and Cypriots namely Mediterranean people In Italy there appears to be two areas in which the disorder is most common *(18)* These are Sicily where 4 45 per cent *of the people show the trait and in northern Italy* around the Po delta where 10 2 per cent are said to have evidence of the disease From a survey of hospital records in the Italian element of the city of Rochester New York it was estimated by Neel and Valentine *(19)* that thalassemia occurs once in 2364 births in women of Italian descent and the incidence of the genetically related condition thalassemia minor is once in each 25 persons of this group

Isolated cases of both thalassemia major and minor have been reported in other races namely *Jews English Egyptians Indians Anglo Indians Chinese Negroes American Indians and Filipinos* For a comprehensive discussion of this phase of the disease the reader is referred to the publication by Neel *(20)* According to this observer there can be no doubt

of the occurrence in non Mediterranean people of clinical syndromes which are undistinguishable from thalassemia It is not certain that all of these cases have the same genetic basis but it is probable that at least a portion represents the same disease This same observer states that no reason is known for the geographical distribution of the condition

Heredity —As persons with thalassemia rarely, if ever survive to the age when they reproduce it is at once suggested that the disease must be transmitted mainly by those persons with thalassemia minor type of the disorder The occurrence of many or all of the manifestations of thalassemia minor in parents of children who have thalassemia major suggests that the disorders might be related genetically It has been conclusively demonstrated in recent years that the *mild disease usually results from a heterozygous condition from the same gene which is responsible for the severe disease when it is homozygous* * Or as Neel states (*21*) There is an incompletely dominant gene which in the heterozygous state results in the mild anemia in the homozygous state it results in the more severe disease (*9 11 22 10 12*)

In other words the severe disease arises in the offspring when both parents transmit the gene whereas the mild disease appears when the gene is transmitted by only one parent The evidence for this is given by Neel as follows first the usual occurrence of the mild disease in both parents of a child with thalassemia major and second an approximation to a ratio of one normal two mildly affected and one severely affected in sibships segregated for the severe disease

Although there appears to be a satisfactory clear distinction between the two conditions there does occur occasionally an intermediate" type which is probably due to environmental factors affecting persons with either the thalassemia minor or major disorders This may result from a striking hemolytic element from dietary deficiencies from acute or chronic hemorrhage or from unknown factors Occasionally the parents of an offspring with thalassemia major may not both have conclusive evidence of thalassemia minor These discrepancies may be explained according to Neel (*21*) as a result of the following 1 failure of the thalassemia gene to find expression (incomplete penetration) 2 a discrepancy between the legal and biological parentage 3 a mutation among the gametes of the apparently normal parent and 4 production of thalassemia minor by the interaction of a single thalassemia gene with as yet unrecognized environmental and genetic factors a situation which is known to exist in sickle cell anemia

Nature of the Disease —Although there is an element of hemolysis in the production of the anemia it is agreed that this is not the fundamental

* The genes which determine hereditary traits occur in pairs one of which is derived from the male and the other from the female parent In a heterozygous individual the members of a gene pair are unlike in their attributes namely father and mother contribute genes with differing effects In a homozygous individual the members of a gene pair are alike

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cause Deposits of iron staining granules which are found throughout the body, suggests a disturbance of pigment metabolism but the real factors responsible for the disorder are obscure Cooley s (23) belief is that the disease is probably concerned primarily with some disturbance of metabolic function with a secondary effect on the bone marrow and the reticulo endothelium It seems to be clear that in the early stages of the malady most of the changes in the red blood cells are lacking

Whipple and Bradford (8) believe that the cause is concerned with an inherited defect which involves the hematopoietic and osseous systems They suggest that it may be a deficiency of a vitamin or endocrine nature acting in a manner similar to the deficiencies of pernicious anemia scurvy or acromegaly They also call attention to the fact that the peculiar pig ment distribution is seen in only one other condition namely hemochro matosis Valentine and Neel (9) also consider that the basic defect which is the fundamental cause of the disease is an inherited inability to utilize or synthesize some substance necessary to normal hemopoiesis According to these observers comparable situations have been described in recent years in both animals and plants and in some instances it has been pos sible to recognize and supply the deficient elements If this hypothesis is correct it must be admitted that thus far it has not been possible to identify the missing elements in this type of anemia

In Wintrobe s opinion (24) the appearance of the red corpuscles and their increased resistance to saline hemolysis suggests that the inherited defect is one in which corpuscles are formed with an adequate or excessive membrane but with little substance They could be pictured therefore as resembling a half inflated football bladder As a result the cells are able to absorb more fluid than normal cells without bursting The other characteristics he believes can be explained by the assumption that they are due to attempts to compensate for faulty red cell formation

In some respects Mediterranean anemia appears to be related to sickle cell anemia and congenital hemolytic jaundice as it is familial and seems to be due to an inherited defect

In a recent study (25) Hamilton and his associates conclude that the fundamental nature of Cooley s anemia has not yet been determined They state that on the basis of clinical and hematological studies several possible mechanisms of production must be considered The presence of jaundice and reticulocytosis suggests a hemolytic type of anemia On the other hand a hyperbilirubinemia is not necessarily present and hemolytic crises do not occur The possibility that a metabolic disorder which causes production of defective erythrocytes must be kept in mind because the necropsy findings are similar to that of hemochromatosis The red blood cells are small bizarre in shape and contain only small amounts of hemoglobin It is thought that the defective erythrocytes must be elim nated from the circulation more rapidly than normal cells The work of Hamilton and his associates (25) furnishes new information relative to

some of these possible causes of the anemia They found that 1 normal erythrocytes transfused into a patient with Cooley s anemia and into a patient with the Cooley s trait survived a normal length of time and 2 although red blood cells from a patient with the trait when transfused into a normal person survived a normal length of time those from a patient with the more severe form of Cooley s anemia survived for a shorter period (85 days) Cells from the same donor with severe Cooley s anemia had a survival period considered to be in the lower range of normal (100 days) when transfused into a patient with Cooley s anemia As the survival period of the cells of Cooley s anemia was calculated to be shorter than normal it was concluded by these investigators that the disorder in Cooley s trait is due to an intrinsic defect in the erythrocytes which shortens the survival time in the circulating blood Increased erythropoiesis however may compensate for the loss and reduction in the number of erythrocytes in the circulating blood may not appear If however the increased destruction is combined with an insufficient rate of erythropoiesis then Cooley s anemia or thalassemia major is produced

It has been found by Kaplan Zuelzer and Hoogma (26) that erythrocytes from patients with Mediterranean anemia when transfused into normal recipients have an *abnormal survival time* which is characterized by an accelerated elimination of 25 to 50 per cent of the cells and a normal survival of the remainder On the other hand the red blood cells from persons with the carrier state of Mediterranean anemia and from one child with an anemia of iron deficiency had normal survival times when transfused into normal recipients Furthermore they noted that normal erythrocytes had normal survival periods when transfused into patients with Mediterranean anemia They conclude that there is a hemolytic component demonstrated by a study of erythrocyte survival which is active in the causation of Mediterranean anemia This increased rate of hemolysis is due to an intracorpuscular erythrocyte abnormality which is not apparent in the carrier state of the disease and is not related simply to a quantitative defect in erythrocyte hemoglobin It is suggested by these investigators that Mediterranean anemia is due to a rapid destruction of erythrocytes in which the basic defect in ultrastructure or composition is associated with pronounced deformities in shape These changes cause them to be destroyed rapidly while the remainder have a normal survival time

It appears clear therefore that one important factor in the production of Mediterranean anemia is the unidentified defect in the erythrocytes which causes them to be more susceptible to hemolysis This appears to be on a hereditary basis but the nature of the defect still remains obscure

Pathology —The patient may have a generalized edema at necropsy which has the anemia as the most likely basis The anemia is also probably the explanation of the fatty changes which are observed in the liver,

cause Deposits of iron staining granules which are found throughout the body suggests a disturbance of pigment metabolism but the real factors responsible for the disorder are obscure Cooley s (23) belief is that the disease is probably concerned primarily with some disturbance of metabolic function, with a secondary effect on the bone marrow and the reticulo endothelium It seems to be clear that in the early stages of the malady most of the changes in the red blood cells are lacking

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Despite his physical handicaps he is in the ninth grade of school and is an honor student

As emphasized by Baty *et al* (3), the general appearance of these patients is so striking that a presumptive diagnosis can be made by inspection alone They state that they bear a greater resemblance to each other than they do to members of their own family There is a moderate degree of pallor of the skin and mucous membranes with a sallow but not icteric tint This has been described as "muddy" which possibly results from the combination of racial color of the skin and pallor although possibly iron

Fig 46 –Eight year-old boy of Italian parentage with erythroblastic anemia Note *the barrel chest protuberant abdomen, and the mongoloid expression of the face* The head shows prominent parietal and frontal bosses and appeared enlarged There is a saddle nose and slightly slanting eyes The spleen and liver were greatly enlarged as outlined in the photograph The red blood cell count was 800 000 per cubic millimeter and the hemoglobin 15 per cent The patient had a subicteric tint and the van den Bergh indirect reaction was less than 1 5 mg per 100 cc. of plasma (Flynn courtesy *British Journal of Radiology*)

deposits in the epidermis may be of some importance in this connection Certain characteristics at once attract attention 1 the features are mongoloid as indicated by prominent eyes sometimes an epicanthal fold high malar bones a short nose with a depressed bridge and the peculiar muddy pallor 2 the head is large and irregularly shaped with prominent frontal and parietal bosses in long standing cases there may be a sulcus like depression in the upper surface of the skull along the

heart and kidneys According to Whipple and Bradford (8) the deposits of iron containing pigment are just as characteristic of the disease complex as any other factor They simulate hemochromatosis in the adult Abundant depositions of iron are found in the liver pancreas lymph glands, gastric mucosa endocrine glands and elsewhere in the body The heart is often enlarged and this may be attributed to the long standing anemia which is also commonly accepted as the cause of cardiac hypertrophy in sickle cell anemia The liver is increased in size and may contain 10 times as much iron as normal There is usually pronounced splenomegaly and infarcts and adhesions are commonly present The gross picture suggests a chronic process Evidence of metaplasia and marrow activity is usually found in some areas of the spleen with myelocytes nucleated red blood cells and megakaryocytes The bones show two types of changes namely an atrophy of the trabeculae and shafts of various bones and a delicate proliferation of new bone in association with thickening of the calvarium which produces the typical markings in the roentgen ray The ribs may show this same type of thickening

The bone marrow characteristically is hyperplastic as in pernicious anemia and the primitive stem cells are abundant Nucleated red cells myelocytes and megakaryocytes are numerous Phagocytes are present and may contain iron pigment Foam cells are observed in small islands and there may be areas of fibrosis

Symptoms and Signs—As previously defined Cooley s anemia Mediterranean anemia or thalassemia is the severe form of the disease which frequently terminates fatally in infancy or childhood Thalassemia minor on the other hand is the carrier state of the severe form and is often asymptomatic or is associated with only mild symptoms which may not seriously impair an individual s normal activities

The onset is gradual and occurs during infancy or childhood Undoubtedly the disease has been present for some time when the first symptom which is usually pallor comes to the attention of the parents Often this is associated with a yellowish tint but it is usually without sufficient intensity to be called jaundice Early in the disease the spleen becomes enlarged It is frequently observed by those in association with the child and may be the chief complaint With the pallor and progressive protuberance of the abdomen there is increasing weakness ease of fatigue and general malaise It is not uncommon to have unexplained episodes of fever for which no cause can be found Other complaints may be anorexia occasional vomiting pain in the upper abdomen dyspnea on exertion and enlargement of the head Pathological fractures are rare but they have been known to occur

Physical examination usually shows that the patient is well nourished but commonly growth is retarded after the first year of life Mentally the patients are normal A patient who has recently been under my observation is now 14 years of age and has had the disease since early childhood

extent that is observed in the spleen It is usually two to three finger breadths below the right costal margin

It is of interest that leg ulcers similar to those seen in sickle cell anemia and congenital hemolytic anemia have been observed in patients with Mediterranean anemia by Estes Farber and Stickney (27) They report that the outstanding histologic feature noted at biopsy of one of these ulcers is the prominent deposition of iron in the cutis It is the opinion of Grendel (28) that the association of leg ulcers with various diseases of the blood is related in some unknown manner to either splenomegaly or hyper

Fig. 48 - Roentgenogram of the skull of the patient shown in Figure 46 There is a radial arrangement of bone spicules in the calvaria Trabeculae connecting the inner and outer tables give the appearance of hair standing on end This is the characteristic appearance of the skull in some patients with erythroblastic anemia (Flynn courtesy British Journal of Radiology)

function of the spleen He reported leg ulcers in one patient with hemolytic anemia and another with pancytopenia (secondary hypersplenism) in association with congestive splenomegaly due to cirrhosis of the liver

Roentgenological Findings in Erythroblastic Anemia—As the bone marrow in this disease is hyperplastic and overactive in an effort to compensate for the anemia it is to be expected that changes would occur in the skeletal system which could be demonstrated in the roentgenogram In the cranium there is characteristically thickening of the vault as

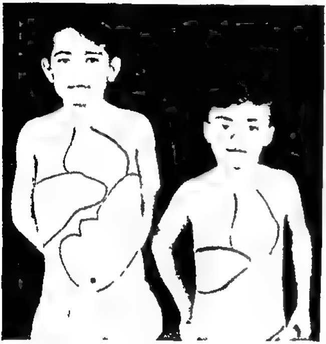

Fig 47 —The boy on the left age 14 years is of Greek parentage and has the fully developed clinical picture of erythroblastic (Cooley or Mediterranian) anemia Note the greatly enlarged heart liver and spleen with the protuberant abdomen The features are mongoloid with a prominent epicanthal fold and slight but definite slanting of the eyes The boy on the right age 8 years is of a family originating in Holland and definitely of non Mediterranean stock He is one of dissimilar male twins who has a severe hypochromic anemia resembling that seen in erythroblastic anemia A splenectomy had been performed at the age of 7 years and many blood transfusions had been given An older brother is said to have similar type of anemia and two other brothers died of anemia at about 3 months of age The features of this patient are somewhat mongoloid but this does not show to a good advantage in the picture In this family the anemia has occured in males exclusively and has been transferred through five generations only by females I am indebted to Dr Wayne Rundles for the picture and data concerning the anemia in the 8 year old boy

superior sagittal suture line due to a widening of the diploe on either side 3 the stature is small and the general body development is retarded and 4 there is often a striking prominence of the abdomen

The peripheral lymph nodes are frequently slightly enlarged They are usually observed as non tender small discrete glands usually in the inguinal and cervical regions but they are also found in the axillae and epitrochlear regions

When the patients are first observed there is almost always enlargement of the heart and a hemic murmur

The abdomen is commonly protuberant and asymmetrical for the enlargement is greater in the upper regions and especially on the left side due to the enlarged spleen The veins may be prominent and there is not infrequently an umbilical hernia resulting from increased abdominal pressure Splenomegaly is present to a variable degree depending upon the stage of the disease for it becomes more pronounced as the condition progresses The spleen may reach only slightly below the costal margin in the early cases but project to the brim of the pelvis or lower when the condition is advanced The liver is also increased in size but not to the

Fig 50 —Chest roentgenogram of a patient age 6 with erythroblastic anemia which shows the grossly enlarged heart The osteoporosis of the bones especially of the clavicles is also apparent (Flynn *British Journal of Radiology*)

severe case observed by Caffey were osteosclerotic in nature due to late increase in cancellous bone In two mild cases with a late onset there were no changes in the skeleton

The Blood —In the early stages of the disease the blood shows no distinctive features The large number of normoblasts in the circulating blood which are so typical of the condition appear later The red blood cell count averages between 2 and 3 millions per cubic millimeter and the hemoglobin between 20 and 40 per cent The anemia is characteristically of the hypochromic microcytic type A young boy 14 years of age of Greek parentage whom I had under my observation several years ago had a red blood cell count of 1 9 per cubic millimeter with a hemoglobin of 14 per cent (2 2 grams per 100 cc) The mean corpuscular volume in this case was the lowest I have ever seen being 47 cubic microns This was because there was a great deal of fragmentation of the erythrocytes and hence many extremely small cells were present in the circulating blood

When the condition is fully developed in addition to erythroblastosis there is polychromatophilia extreme poikilocytosis and anisocytosis

a result of widening of the diploic spaces while the tables are usually thin In early cases of the disease the skull may show only slight thickening with diffuse osteoporosis When the condition is well established, there is a wider diploic space (2 to 25 millimeters) with a striking appearance caused by vertical striations at right angles to the inner tables ("hair on end" appearance) The outer table in such cases may be absent The non striated portion of the skull may have a spongy osteoporosis. The long and short tubular bones show uniform widening of the medullary canals and the cortices are thinned and spread apart The bones are generally osteoporotic Heavy trabeculations especially near the ends of the shaft are often seen to cross irregularly through the medullary spaces The flat bones may also be osteoporotic, but with

Fig 49—The long bones in erythroblastic anemia show generalized osteoporosis The cortex is thin and the medullary cavity widened with conspicuous transverse lines The metacarpals have a rectangular appearance due to pronounced expansion of the medullary cavity The mosiac patterns of the metacarpal bones are well shown (Flynn courtesy British Journal of Radiology)

increased reticulation and a fan like radiation Typical changes therefore may be seen throughout the skeleton with the same findings in the epiphyses as in the advanced cases

In a comprehensive study and review of the literature Caffey (29) in addition to describing the changes which are found throughout the skeleton in the fully developed cases emphasizes the importance of the early alterations He states that the earliest lesion of the skull is a thickening of the lower frontal squamosa Radial striations develop first in the anterior portion of the parietal bones near the saggital suture The frontal bone is the site of the initial and most pronounced thickening He regards the initial lesion of the long bones as a dilatation of the medullary canals with simultaneous atrophy of cortical and cancellous bone Reticulation in the long bones appears several months after the first changes are apparent The late skeletal changes in a long standing

Fig 50 —Chest roentgenogram of a patient age 8 with erythroblastic anemia which shows the grossly enlarged heart The osteoporosis of the bones especially of the clavicles is also apparent (Flynn *British Journal of Radiology*)

severe case observed by Caffey were osteosclerotic in nature due to late increase in cancellous bone In two mild cases with a late onset there were no changes in the skeleton

The Blood —In the early stages of the disease the blood shows no distinctive features The large number of normoblasts in the circulating blood which are so typical of the condition appear later The red blood cell count averages between 2 and 3 millions per cubic millimeter and the hemoglobin between 20 and 40 per cent The anemia is characteristically of the hypochromic microcytic type A young boy 14 years of age of Greek parentage whom I had under my observation several years ago had a red blood cell count of 1 9 per cubic millimeter with a hemoglobin of 14 per cent (2 2 grams per 100 cc) The mean corpuscular *volume in this case was the lowest I have ever seen* being 47 cubic microns This was because there was a great deal of fragmentation of the erythrocytes and hence many extremely small cells were present in the circulating blood

When the condition is fully developed in addition to erythroblastosis there is polychromatophilia extreme poikilocytosis and anisocytosis

The reticulocytes are usually increased in the vicinity of 5 to 10 per cent. Of great importance, from the standpoint of diagnosis, are macrocytes which are usually present, and in some instances assume a high size. Three varieties of these cells are observed. One type has been designated as a "target cell" on account of its deeply stained center and a periphery which is arranged in concentric light and dark zones. The second type is a round or sometimes a slight oval cell with an extremely narrow rim of hemoglobin and a large central area of achromia. The third and most characteristic macrocyte of the disease is a large pale red cell which contains irregularly distributed hemoglobin arranged in clumps and whose intervening areas stain imperfectly. All three types of macrocytes are extremely thin.

The exact significance of "target cells" is not known. It should be kept in mind that they occur in conditions other than erythroblastic anemia. Valentine and Neel *(9)* mention that they are observed in patients with sickle cell anemia, with disease of the liver, with steatorrhea and following splenectomy. They have personally seen such cells in patients with obstructive jaundice, Laennec's cirrhosis, catarrhal jaundice and metastatic involvement of the liver. It is pointed out by these observers that in the carrier state of thalassemia the blood smear may vary from one in which target cells are abundant to one in which there are excessive numbers of oval cells with rare target cells.

The presence of nucleated red blood cells is the characteristic finding from which the disease derives one of its names, erythroblastic anemia. These are typical and immature normoblasts and microblasts. There may be two or three times as many nucleated red blood cells as there are white blood cells.

In the experience of Kato and Downey also *(30)* the most characteristic finding in the blood of Cooley's anemia is the comparatively large number of immature normoblasts in the circulating blood. All stages of erythropoiesis are observed in the blood stream. In addition, the extreme irregularity in distribution of the hemoglobin in the immature erythrocytes, the striking anisocytosis with the less marked poikilocytosis and the moderate amount of polychromasia are the general characteristics of the erythrocytes in their opinion.

The leukocytes are increased in number, usually varying between 10 000 and 25 000 per cubic millimeter, although counts as high as 100 000 per cubic millimeter have been recorded. One wonders, however, if in some of these reported high white blood cell counts the nucleated red blood cells have not been enumerated erroneously as leukocytes. There may be myelocytes and occasionally myeloblasts present but they are usually observed in only small numbers.

There are no significant changes in the platelets.

In most instances there is *increased* resistance of the red blood cells

It has been reported that occasionally hemolysis is not complete in 0.2 per cent salt solution or even in distilled water.

The icterus index is often elevated, usually between 8 to 30 units, and there is a corresponding increase in the blood bilirubin.

The urine may show a urobilinogen content above normal, which has been interpreted as evidence of abnormal hemolysis.

Studies on the cell morphology in eight cases of Mediterranean anemia by Bradford and Dye (*31*) have demonstrated that undoubtedly these patients have a microcytic hypochromic anemia, as shown by the volume measurements, despite the possibility that the extreme fragmentation might introduce some error into the calculations. They found that the mean corpuscular volume was less than normal, usually being below 70 cubic microns, and that the mean corpuscular hemoglobin concentration indicated a hypochromic anemia, as the values were less than 30 per cent and generally below 28 per cent. Cell thickness calculated by the three dimension chart of Von Boros did not show that the cells were much less than normal in thickness. They regard normal thickness measured by this method as 2.1 microns, and in 6 patients the measurements were as follows in microns: 2.1, 1.35, 2.3, 2.05, 2.07 and 2.0 (*31*).

Thalassemia Minor.—In the United States in 1940 and 1941, about 15 years after Cooley had described Mediterranean anemia as a clean-cut clinical entity, another closely associated hematological disorder was noted independently by Wintrobe and his associates (*17*), Dameshek (*16*), and Strauss *et al.* (*32*). This condition had many features in common with thalassemia major but was characterized chiefly by a mild anemia which was for the most part asymptomatic. Both Italian and Greek observers likewise noted certain abnormal findings in the circulating blood of other relatives of patients with the major disease (*33, 34*). According to Neel (*35*), when the initial American reports of thalassemia minor appeared in 1940 (*16, 17*), emphasizing the similarity of this condition to what was then known as Cooley's anemia, Italian students of the disease promptly recognized that the mild type of Cooley's anemia was a closely related condition (*36*). A careful study of the two disorders revealed that thalassemia minor was the carrier condition. Its relationship to thalassemia major was clarified by the studies of Dameshek (*11*) and Valentine and Neel (*9, 22*). On the basis of statistical studies, a hypothesis was formulated which considered that there was a homozygous-heterozygous relationship with the mild condition, to which the name thallassemia minor was applied, representing the heterozote, and that the severe disorder corresponded to the homozygote. (This is discussed fully under the heading of Heredity, p. 505.)

Clinical Features of Mild Types of Mediterranean Anemia (Thalassemia Minor).—Recognition of patients with this form of the disorder is important for at least two reasons, as follows: 1. the patient with

thalassemia minor is a potential source of transmission of the disease and 2, they may present the blood picture of achromia of the red blood cells and on the basis of an incorrect diagnosis may be treated with iron which is completely ineffective As there are over 5 000,000 persons in this country of Mediterranean origin (37) and as it has been estimated that there is an incidence of one in 25 of thalassemia minor in persons of such origin the importance of the problem is readily apparent

According to Smith (37) the diagnosis of the mild type of the disease depends on the evaluation of information from a variety of sources as follows

1 Individuals are usually of Mediterranean origin, chiefly Greek or Italian

2 They are asymptomatic, mildly anemic or without anemia

3 The examination of the blood shows hypochromic macrocytes, basophilic stippling oval and target cells and polycythemia

4 Morphologic alterations in the erythrocytes far exceeds that anticipated from the degree of anemia

5 There is *increased* resistance of the red blood cells to hypotonic solutions of sodium chloride

6 The blood cannot be restored to normal by iron or other forms of antianemic therapy

7 *The trait may be detected in parents and in siblings*

Neel (35) is in accord with the significance of these criteria and adds that as the number of erythrocytes are either normal or increased whereas the hemoglobin and hematocrit are decreased the red blood cells are on the average smaller than normal In other words such persons have a *normal or high red blood cell count with achromia and microcytosis*

In persons with the trait the roentgen changes in the bones are usually slight or inconclusive Occasionally a mild osteoporosis may be present but the characteristic skeletal changes observed in association with marrow hyperplasia are absent There are usually no cardiac murmurs or cardiac hypertrophy nor is there pain in the bones or joints Persons with the mild type are usually of normal appearance but one patient I *observed had the characteristic slanted appearance of the eyes* They are usually asymptomatic the spleen is not enlarged and the condition may escape recognition unless their Mediterranean origin directs attention to the blood One person with thalassemia whom I observed over a period of 10 years persistently had a hemoglobin of about 10 grams and a red blood cell count of approximately 6 0 million per cubic millimeter He maintained that he was free from all symptoms and as evidence of this it can be cited that he was unusually active did not experience *excessive fatigue and served for several years as an* officer on active duty in the United States Army without disability

Treatment—The treatment of Cooley's or Mediterranean anemia is extremely unsatisfactory as it is purely symptomatic. Nothing has been discovered to date which will influence the course of the condition favorably. It is of interest to note that it is one type of microcytic hypochromic anemia which is completely resistant to iron therapy. This metal alone in large doses or in combination with copper, pyridoxin or liver produces no beneficial effect.

Splenectomy is claimed by some to be of benefit because it may produce an immediate but slight and transient improvement in the blood and relieve the child of the weight of a huge spleen. Although more nucleated red blood cells may appear in the circulating blood following this operation and a slight increase in the number of red blood cells occurs, experience indicates that the results are not permanent and hardly worth while. Improvement, however, following splenectomy is reported by Govan (38). There is some evidence to suggest that blood transfusions are required less frequently after splenectomy.

Roentgen ray therapy has been tried without demonstrable improvement but this form of treatment has not had a sufficient trial and should be used in more cases before a final conclusion is reached in regard to its value.

Blood transfusion is useful, in fact, it is the only therapeutic measure which is known to accomplish good but the effect is only transient and no permanent improvement occurs following its use.

Whipple and Bradford (8) tested the effect of a number of therapeutic substances and made the following statement regarding their effectiveness. The following therapeutic measures which we believe have been adequately tested failed to modify the clinical picture. Blood transfusion, plasma and cell extracts, primary and secondary liver extracts, fetal liver extract, spleen extract, raw pancreas, adrenal cortex extract (cortin), estrogenic substances (progynon), vitamin B_1 concentrate, iron and copper.

Prognosis and Course—The severe form of the disease, once established, usually progresses without remission to a fatal issue. If the onset is at an early age, the period of time until the patient succumbs is less. According to Baty, Blackfan and Diamond (3) if the onset is within the first year of life, death often occurs within six months. All of Cooley's cases died within 10 years after the disease was discovered. In general, it can be said that the malady usually begins in infancy, often continues throughout childhood but rarely is there survival until adult life. It seldom, if ever, occurs that a patient with the severe form of the disease survives to an age when reproduction is possible. In the average case the onset is in infancy, the symptoms gradually progress over a period of months or several years and eventually the patient succumbs to an intercurrent infection to which they are peculiarly susceptible or to cardiac complications. With the ease with which blood

transfusions can now be given and with the effectiveness of antibiotic therapy in infections it is possible that such patients may survive for somewhat longer periods. The outlook in such cases, however, must always be considered as poor for sustained improvement and survival despite all forms of therapy

Patients with the mild form of the disease, thalassemia minor certainly may survive to adult life and probably in many instances live their normal span of life with few if any symptoms The possibility of transmitting the disease however should be considered in those who are carriers of the condition Previously it has been suggested by Caminopetros (*34*) that carriers of the trait should be advised against marriage It has more recently been suggested by Silvestroni and Bianco (*14*) that *it is sufficient to discourage marriage between persons who are both carriers of this disorder*. From our present knowledge of the hereditary aspects of the condition this appears to be sound advice

Secondary Erythroblastic Anemia —The term secondary erythroblastic anemia is employed by Higley (*39*) to indicate that such a condition may occur in the adult secondary to some other disease Some of the conditions which have been reported as producing or accompanying an erythroblastic blood picture are

1 Excessive exposure to roentgen ray or radioactive material
2 Chemical or drug poisoning
3 Malignancy with metastases to the bone marrow
4 Chronic diarrhea as found in rickets scurvy or steatorrhea
5 Recurrent and severe hemorrhage
6 Chronic or severe infections
7 Malformation of the circulatory system such as congenital heart disease or arteriovenous aneurysms
8 Hemolytic anemias
9 Extramedullary hematopoiesis (associated with enlargement of the liver and the spleen)
10 Myelogenous leukemia
11 Multiple myeloma
12 Myelosclerosis and myelofibrosis of obscure etiology
13 Marble bone disease of Albers Schonberg
14 Polycythemia
15 Agnogenic myeloid hyperplasia of the spleen

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CHAPTER XII

ERYTHROBLASTOSIS FETALIS

Synonyms—Erythroblastosis neonatorum hydrops fetalis icterus gravis congenital anemia of the newborn erythroleukoblastosis fetal leukemia

Definition—The syndromes of hydrops fetalis, icterus gravis, and congenital anemia of the newborn although presenting different clinical pictures are included under the general term of erythroblastosis fetalis This is because the three conditions have in common the following characteristics a hemolytic anemia of varying severity, occurring in utero or within the first few days of extrauterine life due to destruction of erythrocytes by specific antibodies of maternal origin by extensive extramedullary hematopoiesis the presence of numerous nucleated red blood cells in the circulating blood (erythroblastosis) hepatomegaly and splenomegaly and by the fact that successive members of the same family may show evidences of any one of the three clinical types of the disease

History—The term erythroblastosis fetalis is employed to describe three somewhat dissimilar clinical conditions all of which have the same blood picture of excessive hemolysis and abnormal hemopoiesis The historical aspect of the subject therefore must necessarily be concerned with tracing the development of our knowledge concerning each one of the three somewhat different separate clinical entities They have been known in the past as universal fetal hydrops familial icterus gravis and certain cases of congenital anemia

The best known early monograph dealing with universal edema of the fetus is that of Ballantyne (*1*) who in 1898 collected 70 cases the first being recorded in 1614 The exact nature of the disease condition in some of the cases in this group is not known but the presence of an enlarged liver and spleen suggest that there was an associated disturbance of the blood In 1905 (*2*) Swart described a newborn infant with generalized edema in which there was extramedullary formation of the blood in the liver the spleen and the kidneys but apparently he did not appreciate the significance of the associated abnormal blood formation at that time A somewhat similar instance was reported by King (*3*) To Schridde (*4 5*) in 1910 must go the credit for first describing the occurrence of certain universal types of edema in infants associated with the causative disturbance of the hematopoietic organs Rautmann (*6*) applied the name erythroblastosis" to the underlying hematological condition

Early cases of icterus gravis neonatorum were reported by Blomfield (7) Arkwright (8), and others but they mentioned only the familial incidence the intensity of the icterus, and the ominous outlook and failed to recognize the underlying pathology of the condition The erythroblastosis was first recognized as a part of the clinical picture by Buchan and Comrie in 1919 (9) These authors studied the incidence of the disease in two families in which several newborn infants developed icterus gravis The presence of large numbers of nucleated red blood cells in the circulating blood was noted at birth Furthermore they observed the splenomegaly and hepatomegaly and the presence of extramedullary foci of blood formation De Lange and Arntzenius (*10*) first directed attention to the occurrence of dark yellow amniotic fluid and a vernix caseosa of a saffron yellow hue at the birth of patients suffering from this disease

The presence of an unusual type of anemia in newborn infants was reported by Finklestein in 1911 (*11*) and others In 1909 Buchan and Comrie (9) observed the presence of a severe anemia in four of the infants they studied at birth Priority for the recognition of the anemia alone however is usually accorded to Ecklin (*12*) who described in 1919 a severe case of anemia in the new born

In 1932 Diamond Blackfan and Baty (*13*) gave an excellent review of the literature dealing with the subject and reported the details concerning 20 cases They concluded that universal edema of the fetus familial icterus neonatorum and anemia of the newborn are closely related conditions which are dependent upon the same underlying process The literature dealing with the theories concerning the study of the disorder prior to the development of the modern concept has been summarized by Darrow (*14*)

Following the discovery by Landsteiner and Wiener (*15*) of the Rh factor epoch making studies which elucidated the cause of erythroblastosis fetalis were instituted Of greatest importance were the observations of Levine and Stetson (*16*) and others (*17 18, 19 20*) dealing with the cause of inter group transfusion accidents associated with pregnancy which established the importance of the concept of iso immunization of the mother by factors in the blood of the fetus transmitted by the father From these studies arose the present day conclusions concerning the etiology of erythroblastosis fetalis In a publication in 1941 Levine Burnham Katzin and Vogel (*19*) concluded that in 93 per cent of the cases erythroblastosis resulted from iso immunization of the Rh negative mother by the Rh factor in the erythrocytes of the fetus They further concluded that the pathologic manifestations of the disease resulted from the intra uterine action of the maternal immune agglutinins on the susceptible red blood cells of the fetus and finally that intra group transfusion accidents associated with pregnancy could be prevented by the use of Rh negative donors and the cross matching test

An important article with a selective bibliography dealing with the history of the rhesus blood types has been published by Wiener (21)

Etiology —It has now been accepted by all students of the disorder that erythroblastosis fetalis results in almost all instances from destruction of the fetal red blood cells due to the action of specific antibodies of maternal origin These are stimulated by the leakage of the Rh positive red blood cells of the fetus through the placental villi during pregnancy In a recent study by Wiener Nappi and Gordon (22) it was found that of 211 babies from sensitized mothers 23 were Rh negative and 168 were Rh positive None of the Rh negative babies had erythroblastosis fetalis whereas 90 per cent of the Rh positive infants were affected They conclude that there is a definite correlation between the height of the titer of the maternal Rh antibodies antenatally with the severity of the disease and the mortality rate In other words typically the Rh negative woman develops Rh antibodies as the result of a pregnancy with an Rh positive infant in utero or less commonly due to a transfusion with Rh positive blood

A study of the mode of transfer of the incompatible fetal red blood cells from the fetus to the mother and of the antibodies from the mother to the fetus has been made by Kline (23) He concludes that examination of placentas from pregnant women in whom erythroblastosis has developed in the fetus show changes in the villi which would permit contact of the adjacent maternal blood with the fetal circulation

Although antibodies develop in the Rh negative pregnant woman almost always because of the introduction of red blood cells which are Rh positive in a few cases they form as a result of A B incompatibility For example in a study of 338 Rh negative mothers who did not have Rh antibodies in their circulating blood it was found by Wiener Nappi and Gordon (22) that there were two infants with mild erythroblastosis fetalis which was attributed to an A and B sensitization Apparently anti A and anti B agglutinins are not harmful to the red blood cells of the fetus usually because of their low titer Occasionally however as when an untoward reaction occurs in an adult from the use of an O donor the titer may be high and the fetal erythrocytes are hemolyzed

Relation of Hereditary Aspects of the Rh System to Erythroblastosis Fetalis —No attempt will be made to enter into a discussion of the intricate details of the Rh system and its relationship to erythroblastosis fetalis Admirable and extensive discussions dealing with this important topic are given by Wiener (24) Mollison (25) Pickles (26) and by Andresen (27)

It should be emphasized that the Rh antigen initially described has been given the designation of Rho or D It is agreed that this antigen is capable of stimulating antibody formation more effectively than any other one and furthermore that it accounts for almost all cases of

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In 1932 Diamond Blackfan and Baty (13) gave an excellent review of the literature dealing with the subject and reported the details concerning 20 cases They concluded that universal edema of the fetus familial icterus neonatorum and anemia of the newborn are closely related conditions which are dependent upon the same underlying process The literature dealing with the theories concerning the study of the disorder prior to the development of the modern concept has been summarized by Darrow (14)

Following the discovery by Landsteiner and Wiener (15) of the Rh factor epoch making studies which elucidated the cause of erythroblastosis fetalis were instituted Of greatest importance were the observations of Levine and Stetson (16) and others (17 18, 19 20) dealing with the cause of inter group transfusion accidents associated with pregnancy which established the importance of the concept of iso immunization of the mother by factors in the blood of the fetus transmitted by the father From these studies arose the present day conclusions concerning the etiology of erythroblastosis fetalis In a publication in 1941 Levine Burnham Katzin and Vogel (19) concluded that in 93 per cent of the cases erythroblastosis resulted from iso immunization of the Rh negative mother by the Rh factor in the erythrocytes of the fetus They further concluded that the pathologic manifestations of the disease resulted from the intra uterine action of the maternal immune agglutinins on the susceptible red blood cells of the fetus and finally that intra group transfusion accidents associated with pregnancy could be prevented by the use of Rh negative donors and the cross matching test

An important article with a selective bibliography dealing with the history of the rhesus blood types has been published by Wiener (21)

Etiology —It has now been accepted by all students of the disorder that erythroblastosis fetalis results in almost all instances from destruction of the fetal red blood cells due to the action of specific antibodies of maternal origin These are stimulated by the leakage of the Rh positive red blood cells of the fetus through the placental villi during pregnancy In a recent study by Wiener Nappi and Gordon (22) it was found that of 211 babies from sensitized mothers 23 were Rh negative and 188 were Rh positive None of the Rh negative babies had erythroblastosis fetalis whereas 90 per cent of the Rh positive infants were affected They conclude that there is a definite correlation between the height of the titer of the maternal Rh antibodies antenatally with the severity of the disease and the mortality rate In other words typically the Rh negative woman develops Rh antibodies as the result of a pregnancy with an Rh positive infant in utero or less commonly due to a transfusion with Rh positive blood

A study of the mode of transfer of the incompatible fetal red blood cells from the fetus to the mother and of the antibodies from the mother to the fetus has been made by Kline (23) He concludes that examination of placentas from pregnant women in whom erythroblastosis has developed in the fetus show changes in the villi which would permit contact of the adjacent maternal blood with the fetal circulation

Although antibodies develop in the Rh negative pregnant woman almost always because of the introduction of red blood cells which are Rh positive in a few cases they form as a result of A B incompatibility For example in a study of 338 Rh negative mothers who did not have Rh antibodies in their circulating blood it was found by Wiener Nappi and Gordon (22) that there were two infants with mild erythroblastosis fetalis which was attributed to an A and B sensitization Apparently anti A and anti B agglutinins are not harmful to the red blood cells of the fetus usually because of their low titer Occasionally however as when an untoward reaction occurs in an adult from the use of an O donor the titer may be high and the fetal erythrocytes are hemolyzed

Relation of Hereditary Aspects of the Rh System to Erythroblastosis Fetalis —No attempt will be made to enter into a discussion of the intricate details of the Rh system and its relationship to erythroblastosis fetalis Admirable and extensive discussions dealing with this important topic are given by Wiener (24) Mollison (25) Pickles (26) and by Andresen (27)

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The bone marrow shows active hematopoiesis often in excess of normal which in some cases may cause over-crowding of the marrow spaces There is an unusual and occasionally extreme extramedullary blood cell formation which is considered as abnormal for a full term infant According to Darrow (*14*) the condition is that usually found in a five-month-old fetus The extramedullary hemopoiesis in erythroblastosis and related conditions so far exceeds the normal as to constitute an outstanding characteristic There is an output of young and often quite immature red blood cells not only from the bone marrow but also from the extramedullary foci in the enlarged liver and spleen the kidneys adrenals pancreas lymph nodes thyroid gland and other organs

It should be kept in mind that erythroblastosis as evidenced by a large number of nucleated red blood cells in the circulating blood may develop in infants who do not have hemolytic anemia resulting from Rh incompatibility The condition may also arise according to Diamond (29) in the presence of infection with congenital malformations of the heart with anoxemia due to atelectasis of the lungs and with intracranial hemorrhage and even in extremely premature infants Such conditions may be differentiated from hemolysis due to Rh incompatibility by the demonstration of an Rh negative mother an Rh positive infant and anti Rh agglutinins in the mother s serum

The liver is usually enlarged from two to three times its normal size and contains large masses of hematopoietic tissue predominately erythropoietic scattered in the periportal spaces and within the hepatic sinusoids The spleen is greatly enlarged and engorged with blood Here also many masses of hematopoietic cells are found

Kernicterus as indicated by the yellow staining of the gray matter of the brain with bile is an important finding and is present in one half or more of the patients who succumb in the neonatal period (30) The condition most commonly involves the caudate and lenticular nuclei and the nucleus of Luys and in some instances the dentate nucleus the optic thalamus and the nuclei of the midbrain and medula

Symptoms and Signs —The classification of cases of erythroblastosis based on a study of 47 cases suggested by Javert (*31*) is as follows

Erythroblastosis with hydrops	16 cases
" " icterus	22 cases
" " anemia	3 cases
" " hemorrhagic diathesis	3 cases
(Unclassified) without hydrops icterus or anemia	3 cases

The most important types from the standpoint of frequency judging from the above table are the hydrops and icteric variety which comprise 38 of the 47 cases or 82 per cent The main abnormalities of the infants at birth may be given as follows they are usually larger than

erythroblastosis fetalis In ordinary routine practice therefore it is the only antibody that need be investigated

It has been demonstrated by Landsteiner and Wiener (28) that the Rh factor is inherited as a simple Mendelian dominant by a pair of allelic genes Rh and rh Furthermore it is known that Rh negative persons are always homozygous (genotype rhrh) whereas Rh positive individuals may be homozygous (genotype RHRH) or heterozygous (genotype RhRh) As stated by Wiener (24), Therefore when both parents are Rh negative all children must be Rh negative If one parent is Rh positive and the other Rh negative then either all of the children will be Rh positive (when the Rh positive parent is homozygous) or half of the children will be Rh positive and half Rh negative (when the *Rh positive parent is heterozygous)* *When both* parents are *Rh* positive, then all of the children will be Rh positive except when both parents are heterozygous in which case one fourth of the children will be Rh negative

It is of practical importance therefore in advising a man and wife when the latter is Rh negative to determine by agglutination reactions whether the male is homozygous or heterozygous If the former is the case the possibility of the fetus in utero being Rh positive is 100 per cent and the likelihood of erythroblastosis fetalis developing especially in multiple pregnancies is great On the other hand, if the male parent is heterozygous the chance of the fetus being Rh positive is only 50 per cent and hence the prospect of the baby developing the disorder is less

Racial Variation in Rh Types —There is a considerable racial variation in the incidence of the Rh negative types Data taken from a table prepared by Wiener (*24*) indicate that about 95 per cent or the Caucasian race have Rh positive blood The highest frequency of the Rh negative type among white persons has been found in Australia (17 7 per cent) the lowest among the Canadian Jews (8 6 per cent) There is almost a complete absence of Rh negative types among the Mongolian races (Chinese and Japanese) natives of southeastern Asia and the Pacific Islands and the American Indians Negroes have an Rh negative frequency of an intermediate range (4–8 per cent)

Pathology —At necropsy, infants with the condition reveal characteristically a deep yellow staining of all internal viscera the skin and serous membranes sclerae and fat tissue Other gross changes are the enlargement of the liver and the spleen the pallor which is apparent despite the presence of jaundice and small ecchymotic hemorrhages in the skin and the serous and mucous membranes

There is some disturbance of pigment metabolism as indicated by the presence of large amounts of hemosiderin in the hepatic cells the Kupffer cells of the liver the endothelial phagocytes of the spleen and the epithelial cells of the convoluted tubules of the kidney

this there is a greater degree of jaundice and earlier intra uterine death of the infant with universal hydrops and anemia

In Javert's cases (31) of the 25 infants born alive and having erythroblastosis the following clinical signs were observed edema in 16 cases pallor in 12 skin petechiae in 16 visceral hemorrhage in seven cyanosis in 17 dyspnea in 10 convulsions in four Many of the infants observed by him had two or more of these signs in addition to the hydrops and jaundice

An important complication of erythroblastosis fetalis is jaundice with staining of the brain tissue with bile pigments and subsequent degenerative changes It is a prominent cause of death in the neonatal period and may cause serious neurological manifestations in later life The condition termed *kernicterus* has been defined by Pickles who gives an excellent summary of our knowledge of the disease (26) as a syndrome characterized by extrapyramidal involvement of the central nervous system and mental backwardness observed as a sequel to the yellow staining and necrosis of the brain cells such as seen in infants dying in the neonatal period

Not only is it of importance as a cause of death during the neonatal period but those children who recover from the acute disease have sequelae in about 6 to 8 per cent of the cases with mental retardation and sometimes other evidence of serious brain damage The condition was initially described by Guthrie (32) and its importance emphasized by Fitzgerald Greenfield and Kounine (33) A review of the late neurological sequelae has been made by Vaughan (30)

Blood Examination —Patients with this disorder have an anemia which varies in severity from 0 5 to 3 5 millions per cubic millimeter and a hemoglobin from 3 0 to 13 5 grams per 100 cc depending on the intensity of the disease The anemia is of the macrocytic normochromic type as the mean corpuscular volume is increased above the values for the newborn and the mean corpuscular hemoglobin concentration is within normal limits The striking feature of the blood is the evidences of immaturity of the red blood cells many of which are nucleated There are other indications of immaturity of the erythrocytes as pronounced polychromatophilia red blood cells with nuclear fragments and many (10 to 50 per cent or more) red blood cells containing reticulum The nucleated erythrocytes are chiefly normoblasts although megaloblasts are said to occur Anisocytosis is often observed but poikilocytosis is usually absent With progression of the disease there may be a remarkably rapid decrease in the number of erythrocytes as indicated by a reduction in the total count of as many as a million per cubic millimeter per day

A leukocytosis varying from 25 000 to 50 000 per cubic millimeter is often observed but care should be taken to avoid enumerating the

the normal child averaging 1000 grams more in body weight than the normal infant of 36 weeks gestation at birth the hydropic child is edematous with a protuberant abdomen due to ascites and a large liver as many such children are stillborn, the skin is commonly macerated the child with the icteric form is usually born alive but many require resuscitation, jaundice is either present at birth or becomes apparent shortly thereafter there is almost always enlargement of the liver and spleen

In Javert s group of 47 cases (31) there was an incidence of 21 per cent of congenital anomalies including harelip cleft palate spina bifida hydrocele supernumerary fingers cervical rib urethral stricture and an interventricular septal defect As the frequency of such defects in stillborn and those who succumb shortly after birth is only 0 68 and 0 54 respectively, it is apparent that the tendency to these congenital anomalies is much greater in this condition

It has been emphasized (31) that there may be an overlapping of signs in patients with the different varieties of this disease For instance an icteric infant may develop edema, and both types have a severe associated anemia Also a few infants may die in utero, or may not survive for a sufficient period of time to develop any of the usual signs of edema jaundice or anemia It is usually possible however to separate the different types depending upon the predominance of the various clinical features For example patients with hydrops fetalis have a striking anasarca and effusions into the pleural pericardial, and abdominal cavities In patients with icterus gravis there is jaundice which is present at birth or appears within a few days In congenital anemia the patient is pale but there is an absence of icterus and edema In all three conditions there is a severe anemia with nucleated red blood cells in the circulating blood

According to Diamond (29) the classic symptoms and signs of the disease are jaundice within 24 to 48 hours and the development of an anemia often at birth but more regularly by the third or fourth day This becomes more severe by the end of the seventh or eighth day if the disease is not of the fulminating type A fatal issue from anemia or anoxemia however may ensue within the first 24 to 48 hours In most cases there is splenomegaly and hepatomegaly In the most severely affected infants edema or even universal hydrops may be apparent immediately after birth or within the first day A large number of nucleated erythrocytes occur in the peripheral blood In the more severe forms, the jaundice may be increased rapidly in intensity due to blockage in the bile capillaries and a disturbance of the hepatic cells In some patients the jaundice may be so severe and overshadow all other manifestations of the disease to such an extent that congenital obliteration of the bile ducts is suspected It is known that hemolytic anemia often becomes more severe in succeeding pregnancies With

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nucleated red blood cells in the counting chamber as leukocytes. Occasionally a few myelocytes may be observed.

The blood platelets are usually normal in number but in the severe cases they are significantly reduced giving rise to purpura, a prolonged bleeding time, and poor clot retraction.

Treatment of Erythroblastosis Fetalis.—It is clear that once an Rh negative woman has been immunized, usually as a result of a pregnancy with a Rh positive fetus, or occasionally as a result of receiving Rh positive blood transfusions, the condition is a permanent one. Desensitization does not occur spontaneously nor has any known method been devised by which this can be accomplished.

Hence when such an immunized person becomes pregnant, the likelihood of the child in utero being affected by antibiotics in the maternal blood is considerable. As shown by Potter (*35*) the possibility of the child developing erythroblastosis increases strikingly with each pregnancy. For example, it has been demonstrated that in her series of 18 468 pregnancies observed at the Chicago Lying In Hospital over a period of five years, erythroblastosis occurred during the first pregnancy once in 2814 deliveries, in a ratio of 1 172 in the second pregnancy, and 1 55 for the sixth pregnancy. In her opinion, it is unlikely for an infant to succumb to the disorder who has not had an older sibling affected by the same condition.

It has not been demonstrated that any form of therapy can exert a beneficial effect on the fetus who has the disease in utero. The favorable effects previously claimed of a premature delivery on the basis that the maternal titer is highest in the last trimester of pregnancy is no longer supported by Diamond and his associates (*34*). The recommendation of Wiener (*24*) that prophylactic treatment with typhoid or pertussis vaccine might be helpful has not been universally accepted. He states that the vaccine does not affect the titer of the antibodies already in the serum but that it might help to prevent their reappearance after they have disappeared spontaneously.

The limited use of cortisone in two previously immunized Rh negative pregnant women has been reported by Doerner and his associates (*36*). They observed that the immunized state was not abolished nor was the degree of immunization lessened by the administration of this substance. This medication did not prevent the development of the hemolytic state in the infants delivered by these patients. In one infant to whom cortisone was given, however, it was considered that the objective evidence of the hemolytic process was quickly reversed. They suggest that further observations on the use of cortisone in this condition are warranted. It is possible, in their opinion, that cortisone therapy may be useful in this condition only if given before irreversible tissue changes have occurred.

The Use of Simple and Sedimented Red Blood Cell Transfusions.—Although simple blood transfusions are of use it has been conclusively established that exchange transfusions are superior and hence are the treatment of choice in this condition (*37 38 39 40 41 42 43*)

Simple transfusions of whole blood are undoubtedly useful in this condition because they supply red blood cells to replace those destroyed by the excessive hemolytic process Such transfusions have failed in a considerable number of cases because 1 the amount of blood given has been too small and 2 because of the harmful effects of the adult plasma which has been given as a part of the whole blood

The use of red blood cells which have been permitted to sediment in the containers of a blood bank has been reported by Pennell (*44*) When 50 to 60 cc of sedimented cells separated from the plasma were given to 28 patients with erythroblastosis fetalis there was a mortality of only 10 7 per cent which is a rate comparable to that following the use of exchange transfusions It is claimed by Pennell that the use of such sedimented erythrocytes has the following advantages 1 the severe anemia can be controlled by the injection of a comparatively small concentrated volume of cells (50–60 cc) without overburdening the infant s circulatory system and 2 the procedure is as simple as an ordinary blood transfusion as it does not require special equipment and is available wherever there is a blood bank The method of treatment eliminates the injection of possible harmful substances such as excessive amount of sodium citrate heparin and calcium gluconate which may be employed in exchange transfusions

Exchange Transfusions.—*The Treatment of Choice.*—The use of exchange transfusions in the treatment of erythroblastic infants is the optimum form of therapy although simple transfusions and the use of sedimented erythrocytes are of value Exchange transfusions are especially indicated for the following reasons 1 the antibodies which are the cause of the excessive hemolysis in the infant s blood stream are practically all removed (85 to 90 per cent) 2 the erythroblastic cells are eliminated before they have time for clumping and destruction 3 the damaged erythrocytes are replaced by Rh negative cells which cannot be affected by Rh antibodies and 4 the severity of the jaundice is immediately lessened by the removal of plasma containing an increased amount of bilirubin and hence the possibility of damage to the nervous system (kernicterus) is diminished

It is reported by Wiener (*45*) that in treating 80 cases of erythroblastosis with exchange transfusions there was a mortality rate of only 15 4 per cent as compared to a rate of 70 8 per cent when the patients were treated with ordinary blood transfusions Furthermore in patients receiving simple blood transfusion therapy there were neurologic sequelae in 15 to 30 per cent whereas all of the 66 erythroblastotic infants

who recovered following exchange transfusions developed perfectly normally from a mental and physical standpoint

In a comprehensive article dealing with exchange transfusions Diamond and his associates (*46*) discuss the use of such a procedure in more than 300 infants. They have used polyethylene tubing and a special umbilical vein adapter which permits alternate withdrawal and injection of blood. Usually 500 cc is given in one hour but in very sick babies the injection is prolonged over a period of one and one half or two hours. If the patient's condition is still not satisfactory, then a second transfusion of the same amount is given some hours later. They report complete recovery in 82.4 per cent of the patients and the development of kernicterus in only 5.4 per cent. It is their opinion that exchange transfusion is the treatment of choice in babies with *erythroblastosis fetalis*. They employ blood from Rh negative women as statistical evidence in their opinion supports the more beneficial effect of female blood (*42*). They also recommend the routine use of group O donors on the basis that the baby may be incompatible with the mother in the ABO system, thereby making use of group A or B blood dangerous. Furthermore they advocate the addition of soluble A and B substances to group O blood to an infant in groups A, B or AB in the amount of 10 cc to the pint. It is stated by Diamond and his group that when the baby is seriously ill it has been their custom to proceed immediately with the exchange transfusion using group O Rh negative bank blood to which A and B substances have been added without crossmatch tests although such a test is advisable when time permits.

Indications for Exchange Transfusions.—There is evidence to indicate that 10 to 20 per cent of all Rh positive babies born of sensitized Rh negative mothers will not have clinical evidence of erythroblastosis fetalis such as jaundice or a significant anemia. With few if any, exceptions, however they will have a positive Coombs test (*47*). Nevertheless the failure to treat such an infant may be followed by such serious complications that certain criteria must be employed as indications for exchange transfusions. The following based on the experience of Diamond and his associates are recommended as indications for such a procedure.

1. If an infant less than 24 hours of age has clinical evidence of the disorder such as early jaundice, hematosplenomegaly, pallor, edema, petechiae, or a blood cell count of less than 4.5 millions per cubic millimeter or a hemoglobin value of less than 13.5 grams per 100 cc of blood.

2. If the infant is Rh positive as indicated by direct testing and the mother's titer of Rh antibody has been higher than 1:16 at any time during the pregnancy.

3. If the baby is Rh positive, the mother Rh negative and there is a history of anemia at birth or kernicterus in an older sibling.

4 If the Rh positive infant born of an Rh negative mother is immature with an estimated gestation of less than 38 weeks This indication is based on the observation of Vaughan and his associates (47) of the likelihood of kernicterus in immature infants especially in immature male babies

It is recommended further by Diamond and his associates (46) that a second exchange blood transfusion be given within 12 to 24 hours after the initial one if the possibility of kernicterus seems likely They stress that the premature infant of a highly sensitized mother who has previously had a baby with kernicterus is the most likely candidate for this They also consider the possibility of this complication developing in infants who become intensely jaundiced in the first 12 to 24 hours after an exchange transfusion is done at birth

It has recently been stated by Wiener Nappi and Gordon (22) that in a study of the mortality rate of erythroblastotic babies which included both stillbirths and neonatal deaths there was a close correlation between the death rate and the height of the titer of the maternal Rh antibodies antenatally As an example of this they observed that with titers of four units or less by the albumin plasma method the total mortality rate was 12 2 per cent whereas with titers up to 256 units the total mortality rate was as high as 72 2 per cent They emphasize however that in some instances there may be a discrepancy between the titer and the outlook in any given case and suggest that this may be explained on the basis of variation in the constitutional factors affecting a baby s susceptibility to the antibodies

In evaluating the outlook in any given Rh negative mother when the male parent is Rh positive it is well to keep in mind the observations of Potter (35) who found that the average number of surviving children born to each patient before the birth of an infant with erythroblastosis was 1 4 It is emphasized that in the two years prior to the report no infant born alive has died of erythroblastosis who has not had an older sibling affected by the same disease Furthermore this observer concludes that *the previous maternal history has been of more value in prognosticating the fate of an infant born of an immunized Rh negative woman than have been the changes in the maternal antibody titer or differences in the variety of antibodies present*

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CHAPTER XIII

HEMORRHAGIC STATES DUE TO CHANGES IN THE NORMAL CLOTTING ELEMENTS OF THE BLOOD

Introduction—Since the beginning of our knowledge of the subjects of physiology and pathology scientists have been plagued with the fact that the readily observable phenomena the prompt clotting of the blood when it is shed and the absence of clotting intravascularly, still lacks a complete explanation despite careful investigations over a long period of years and the application of complicated methods to the problem

Despite important recent contributions to our knowledge it is generally agreed that the final word concerning the mechanisms of normal blood coagulation has not been said Hence any theory which is now accepted must be so on a purely tentative basis The multiple terminology, the incompleteness of our knowledge in relation to some of the aspects of the process the unwarranted conclusions based on inadequate data have all added to the present confusion relating to this problem and the pathological deviations leading to abnormal bleeding

Those who attempt to gain an understanding of this process by a survey of the current literature will indeed be bewildered as some aspects of the problem are difficult to evaluate Nevertheless sufficient information is at hand and new and important additions are being made constantly which will undoubtedly clarify the problem in due time For the present it is sufficient to say that enough information is now available to be of great assistance to the clinician It should be kept in mind however that any current theory *relating to this mechanism will undoubtedly* be modified in the future

An extensive resume with a bibliography of over 100 articles dealing with the mechanism of blood coagulation in normal and pathologic conditions has recently been published by Stefanini (*1*)

The so called classical theory of Morawitz (2 3) has served a most useful purpose in the past and still does The original concept considered that the process occurred in two phases as follows

(1) Prothrombin + thromboplastin* + calcium → thrombin
(2) Thrombin + fibrinogen → fibrin

Its incompleteness is now recognized by all who are interested in the

*Also termed thrombokinase cytozyme and thrombozyme indicating that the substance is in the nature of an enzyme

subject of coagulation of the blood. Among other changes it is known that some of the individual factors must now be subdivided. The original plan may be preserved in part, however, for it serves a useful purpose as a basis for an understanding of some of the hemorrhagic tendencies observed in clinical medicine.

According to Quick (4) the principal shortcomings of the theory proposed by Morawitz are: 1, it fails to define the function of the platelets; 2, no explicit explanation of the source of thromboplastin is provided; 3, the action of thromboplastin and calcium is considered to be catalytic; 4, prothrombin is regarded as a unit substance; 5, there is no consideration given to the autocatalytic nature of the coagulation process; 6, no explanation is offered for the maintenance of the fluidity of the blood; and 7, there is no correlation of the coagulation reaction with the generalized mechanisms of hemostasis.

Conversion Factors and Accelerators in the Formation of Thrombin.—The present day concepts of the coagulation of the blood have taken into consideration more than the four factors which Morawitz thought to be the only ones essential to the process; these were thromboplastin, calcium, prothrombin and fibrinogen. To these have been added other factors which Morawitz did not consider. In general these new agents are: 1, concerned with the conversion of prothrombin to thrombin; and 2, the acceleration of the progress of the reaction.

With our present knowledge of the clotting process it must be considered that prothrombin and fibrinogen are the basic material from which the clot forms. There is agreement that prothrombin is converted to thrombin and that this agent converts fibrinogen to fibrin. As had been emphasized by Stefanini (5), who gives an excellent review of the subject, there are at least five other agents which have an important role in the formation of thrombin. They may be divided into two principal groups as follows, namely: 1, conversion factors; and 2, accelerators.

Conversion factors present in plasma which appear essential for the reactions leading to the formation of thrombin have been given the following designations: labile factor of Quick, factor V of Owren, plasma Ac globulin of Ware and Seegers. The term plasma prothrombin conversion factor (PPC F), however, is preferred by Stefanini (5) to all others. Additional terms which have been used for the conversion factor are: thrombogene (6); the component A of prothrombin was the name first given by Quick but later changed by him to the labile factor (7). Fantl and Nance called it the accelerator factor (8). Honorato designated it the co-factor of thromboplastin (9).

There are at least two important points about the conversion factor which should be emphasized. *First*, it is stated unequivocally by Stefanini (5) that ... all of these different factors share similar general properties and are probably identical ... And *second*, thrombin may be

formed from prothrombin, even in the absence of the conversion factor calcium and thromboplastin, although the process is exceedingly slow

The Function of the Plasma Prothrombin Conversion Factor.—The exact role of the Plasma Prothrombin Conversion Factor or Factor V in the formation of thrombin is not entirely known There is a difference of opinion as to whether it acts simply as a catalyst or as an essential participant reacting with calcium and thromboplastin in definite quantitative proportions It appears to be clearly established, however that the plasma prothrombin conversion factor *must* be present in adequate amounts at least in vivo in order for the formation of thrombin to proceed at a rate capable of maintaining a normal hemostatic mechanism In the absence of a normal quota of PPCF, there is a prompt and decisive diminution in the prothrombin activity of the blood (*10*) and serious hemorrhage may develop (*11*)

It should be kept in mind however that evidence is available to indicate that thrombin may be formed from prothrombin in the absence of calcium thromoplastin and the plasma prothrombin conversion factor (*12 13 14*) It has been reported for example by Seegers (*15*), that when purified prothrombin is dissolved in a 30 per cent solution of sodium citrate it becomes activated to thrombin and some activation is observed in 5 10 and 15 per cent solutions It is this observer s belief therefore that prothrombin is activated autocatalytically in concentrated sodium citrate solution thereby demonstrating that prothrombin itself contains all of the structural material required for the formation of thrombin and no additional components need be added by the activators of prothrombin For this reason (*14*) Seegers McClaughry and Fahey believe that Ac globulin calcium and thromboplastin should be regarded purely as catalysts of prothrombin activation and as such they do not contribute material substances to prothrombin activation

This view is considered critically by Stefanini (*5*) who calls attention to the fact that self activation of thrombin is not equally effective at lower concentrations of sodium citrate Furthermore the possible role of protein bound calcium and minute amounts of contaminating materials should be taken into account Apropos of the latter this observer emphasizes that only a small amount of thrombin is necessary to activate PPCF to serum accelerator which greatly accelerates the production of thrombin hence a large amount of thrombin may be formed with very little PPCF In addition experimental evidence is available which lends support to the view that PPCF is essential to the formation and reacts with prothrombin thromboplastin and calcium in definite quantitative relationships

Anyone who has carefully examined the evidence therefore must conclude with Stefanini (*5*) that it is evident that the problem of the role of PPCF during coagulation of the blood is far from settled but the significant point may be made that in vivo at least the presence of this

factor in adequate amounts is indispensable for the adequate formation of thrombin from prothrombin

Plasma Prothrombin Conversion Factor (Factor V, AC Globulin) Deficiency.—In 1947 Owren (*11*) reported the case of a female 29 years of age who was observed first in 1943 with an abnormal tendency to bleed Her family history was irrelevant Since childhood the patient had experienced episodes of purpura severe epistaxis menorrhagia and possibly a minor attack of bleeding from the kidneys At times following prolonged epistaxis the hemoglobin had fallen below 30 per cent necessitating several blood transfusions The physical examination disclosed only evidences of severe hemorrhage The whole blood coagulation time by the capillary method was 15 minutes (normal two to five minutes) bleeding time four and one half to five minutes prothrombin time 70 to 80 seconds (normal 15 to 20 seconds) It was not possible to demonstrate any cause for a hypoprothrombinemia as the liver function tests investigation of the stomach intestinal tract and bile ducts revealed no abnormalities *The condition did not respond to large doses of vitamin K*

In an experimental study of coagulating mechanism in this patient the most important finding was that the addition of prothrombin free plasma to the patient s plasma caused a reduction in the patient s prothrombin time as measured by Quick s method In other words the coagulation time of the patient s plasma could be restored to normal by the addition of 20 per cent of *prothrombin free ox plasma* It was concluded therefore by Owren (*11*) that the patient s blood lacked a substance which is normally present and necessary to normal coagulation and that this substance was not included in the classical theory of coagulation as described by Morawitz in 1904 (*16*) This agent was designated by Owren as Factor V

It is claimed by Owren therefore that pure prothrombin is not converted to thrombin by the action of thromboplastin and calcium alone but that the presence of factor V is required Furthermore it has been demonstrated that the velocity or the conversion increases with greater amounts of Factor V up to a certain limit In his opinion the conversion of prothrombin to thrombin includes two stages as follows (1) the formation from Factor V of the actual prothrombin converting enzyme designated as Factor VI and (2) the conversion of prothrombin to thrombin under the influence of Factor VI in the presence of calcium In other words Factor V is a proenzyme for Factor VI

In a more recent publication however (*17*) Owren states that his previous work leading to the assumption that Factor VI derived from Factor V when acting in conjunction with calcium would convert prothrombin to thrombin is not entirely correct Recent studies have shown that even when thromboplastin is added to a mixture of prothrombin Factor VI and calcium the thrombin formation is slow and incomplete

If, however, in addition a small amount of normal plasma is added the thrombin formation proceeds rapidly This investigator has found that the active factor in normal plasma is protein in nature and it is not identical with prothrombin Factor V antihemophilic globulin, or fibrinogen In the opinion of Owren (17) this substance represents a new clotting agent a component of the complex which converts prothrombin to thrombin Further studies concerned with the preparation and properties of this new agent are now being made by this investigator

In parahemophilia there is a deficiency of Factor V, and this leads to a lack of Factor VI whereas in hemophilia according to Owren there is a lack of free or active thromboplastin (thrombokinase) In both types of deficiency the result is identical namely, a deficiency in the formation of thrombin and consequently, delayed coagulation of the plasma In the opinion of Owren the similarity in the deficiency mechanism of coagulation with the factors in the clinical picture which are common to the two conditions justifies the use of the term parahemophilia for Factor V deficiency

The differential diagnosis between parahemophilia and hemophilia is simple according to Owren because the faulty coagulation in patients with parahemophilia is not returned to normal by the addition of thromboplastin as is the case in hemophilia Furthermore in parahemophilia the prothrombin time as determined by the Quick method is elevated but the prothrombin content of the plasma as shown by the two stage method is normal According to Alexander and Goldstein (18) parahemophilia is congenital or acquired and the bleeding phenomena are indistinguishable from those of hypoprothrombinemia The clotting defect does not respond to vitamin K administration but may be corrected with the transfusion of fresh normal blood or plasma Stored blood may not be effective as the deficient clotting factor is not stable disappearing rapidly in bank blood The beneficial effect persists for only four to five days

A pure deficiency of the labile factor is rarely encountered in the opinion of Stefanini (19) and to date has been described only in the congenital variety of the disorder Depletion of both the prothrombin and labile factor is not infrequent and is usually found in hypoprothrombinemias of leukemia and liver disease

Accelerators in the Formation of Thrombin —*Platelet Accelerator*— In 1912 Bordet and DeLange (20) first described a thermostable impure lipoid derived from platelets (cytozyme) which acted as an accelerator for the conversion of prothrombin to thrombin A similar agent has been reported by Mann and his associates (21) and by Ware Fahey and Seegers (22) Apparently this agent acts in the same manner as the serum accelerator but the two can be differentiated by their chemical characteristics They both have in common a loss of activity when heated at 60 degrees C for one half hour or when stored for twenty four

hours and the capacity to increase the amount of prothrombin in stored plasma

In 1904 Bordet and Gengou (23) first described the existence of a serum accelerator which speeds up the process of formation of thrombin from prothrombin These observations have been studied further by Owren (24) and by Ware Fahey and Seegers (22) More recently Alexander and his associates (25) have reported the presence of a serum prothrombin conversion accelerator (SPCA) which likewise they believe has the capacity to accelerate the conversion of prothrombin to thrombin

According to Stefanini (5) our knowledge of the function of the accelerators in the formation of thrombin is incomplete He believes that they require the presence of both calcium and thromboplastin in order to function He also considers that the platelet accelerators are liberated by the lysis of platelets which initiates the process of clotting whereas the serum accelerators are produced only after the process develops In the opinion of Stefanini (5) the presence of accelerators are concerned with autocatalytic mechanisms associated with the coagulation of blood For a more complete discussion of this process the reader is referred to a classical description by Milstone (26)

THEORIES OF BLOOD COAGULATION

The following are three examples of older theories concerned with clotting of the blood which are no longer tenable It has been proposed by Howell (27) that the function of the thromboplastic substance is to remove an inhibitor which is possibly heparin with which the prothrombin is presumably in combination in the circulating blood and thereby liberate free prothrombin A second theory suggested many years ago by Morawitz (2) considers that the platelet or tissue factor may be an enzyme which activates prothrombin to thrombin and hence he suggested the name thrombokinase Perhaps the simplest and the easiest way to think of the clotting process is to consider the third theory as suggested originally by Bordet and DeLange (20) namely that the calcium the prothrombin and thromboplastic substance actually combine to form thrombin This substance once having been formed reacts with the plasma protein fibrinogen which is in the form of a colloidal solution to form the insoluble gel fibrin which is the end product of the clotting process

Theory of Coagulation of the Blood According to Quick—Data supporting this theory appeared during the years 1946 to 1950 (*10 28 29*) The theory is reviewed by Stefanini (*30*) in an article upon which many of the following statements are based

The clotting process according to Quick may be divided into three phases The first consists of the disintegration of the blood platelets

which liberates an enzymatic agent (thromboplastinoginase) This en zyme like substance changes the inactive form of thromboplastin (throm boplastinogen) *which is present normally in the circulating blood*, into the active form of thromboplastin

Platelets are considered to be indispensable for the clotting process This, Quick believes, is supported by the observation that blood free of contamination with tissue thromboplastin fails to clot if the platelets have been completely removed by prolonged high speed centrifugation Such an opinion is however contrary to the view expressed by Conley and his associates (31) who believe that platelet free plasma will coagulate *if brought into contact with a rough glass surface*

The second phase of clotting leads to the formation of thrombin This agent is the product which results from the reaction between prothrom bin, thromboplastin, the labile factor (plasma prothrombin accelerator factor, component A of prothrombin plasma Ac globulin thrombo plastin co factor and thrombogene) It is the opinion of Quick that thrombin thus developed is a slow process but once this substance is formed an autocatalytic process is set into action The latter has two phases *The one labilizes platelets and hence liberates more of the* enzyme thromboplastinogenase which causes the formation of more thromboplastin The other function is to convert the labile factor into an accelerator factor which has the capacity of greatly increasing the speed of formation of thrombin from prothrombin Some have con sidered the formation of thrombin from prothrombin to be of a stechio metric and others of an enzymatic nature

The third phase of the clotting process is the transformation of the soluble fibrinogen to the insoluble fibrin, and hence the formation of the clot

According to this theory the tendency to bleed in thrombopenia is *due to a deficiency of the enzyme thrombinogenase which is assumed* to be normally liberated by lysed platelets In thrombopenic purpura a minimal amount of *thromboplastinigenase is necessary to cause a firm* clot In hemophilia the essential element which is diminished or lacking according to this theory is thromboplastinogen the inactive form of thromboplastin

The theories of blood coagulation as devised by Quick (4) and by Owren (24) by Ware and Seegers (32) and Stefanini (5) are given in detail in the references indicated

A Consideration of the Normal Elements of the Clotting Process —For many years it was thought that there were only four elements that were *essential to the normal* performance of blood coagulation In 1943 however Quick (33) first became aware that prothrombin consisted of two parts one of which he first designated as Component A and later re named the *labile factor* *In 1944 Owren (24) independently* and with out knowledge of Quick s work in the previous year described a fifth

substances essential to clotting which he named Factor V All evidence now indicates that these two factors as described by Quick and Owren are identical

A brief consideration of the formation and normal functions of these five substances is given in the following paragraphs

Prothrombin.—This substance in the presence of calcium and thromboplastin forms thrombin which converts fibrinogen to fibrin It has recently been established that the liver plays an important role in its formation and furthermore that it cannot be produced in the absence of the dietary factor vitamin K. The exact nature of this relationship is unknown but the possibility that vitamin K may be converted directly to prothrombin by the liver has been suggested although convincing proof of this is lacking at present As suggested by Dam (34) it may be that vitamin K simply forms a part of the prothrombin molecule but this explanation is not considered by him to be the most likely It is suggested also by this investigator that the most plausible explanation at present is the assumption that the action of vitamin K is to enable liver cells to produce prothrombin but the mechanism of this reaction is unknown

Destruction of the liver by disease or in experimental animals is associated with a sudden drop in plasma prothrombin Dicumarol blocks the formation of prothrombin but when the drug is discontinued the concentration of prothrombin in the circulating blood rapidly returns to normal According to Goldstein and Alexander (18) the adult apparently uses and regenerates about 80 per cent of his circulating prothrombin daily

The Constitution of Prothrombin.—Prothrombin is the inactive precursor of thrombin a glycoprotein present normally in the circulating blood in amounts varying from 15 to 20 milligrams per 100 cc of plasma According to Seegers (15) the purified material when fully activated has a powerful clotting ability as a milligram is almost sufficient to clot 2 0 liters of a standardized fibrinogen solution in 15 seconds Prothrombin is constantly present in the blood provided an adequate amount of vitamin K, from which it is derived is present in the diet if it is absorbed normally and if the liver performs its normal function of synthesizing it from this material The isoelectric point of prothrombin is about pH 4.2 in buffer of 0 1 ionic strength (35) It is relatively stable at icebox temperatures

It resembles thrombin in that it is destroyed by heating at 60 degrees C Prothrombin is absorbed by barium sulphate (36) by aluminum hydroxide (37) and by Seitz and Berkfeld filters (38) According to Eagle and Harris (39) it is destroyed by proteolytic enzymes

In 1943 Quick concluded that prothrombin consisted of two factors Component A which is destroyed by storage and Component B which is diminished by dicumarol In 1944 Owren (24) described a component of the plasma which he designated as Factor V It is considered by

Quick (4) that Owren's Factor V and also the substances described by Fantl and Nance (40), and by Seegers and his associates (41), are the same as Quick's which he originally designated as Component A (33) but later renamed the labile factor (42)

It is emphasized by Seegers (15) that prothrombin occupies a dominant position in the clotting mechanism He cites proof to show that prothrombin can be converted slowly into thrombin without the aid of thromboplastin or calcium although such a conversion is exceedingly slow Nevertheless, this investigator has shown that when a pure preparation of prothrombin is placed in a concentrated solution of sodium citrate it will be converted into thrombin in about 16 hours This shows that prothrombin itself contains all of the structural material required for the formation of thrombin and nothing need be supplied by the activators of prothrombin It has been shown, however that the rapid activation of prothrombin to thrombin requires the action of at least three accessory factors namely thromboplastin calcium and the plasma accelerator globulin

Estimation of the Prothrombin Time—The prothrombin time is considered to be the interval required for clotting of citrated plasma when the optimum amounts of calcium and thromboplastin are added In other words the time necessary for clotting under these circumstances is considered to be a measure of prothrombin activity It should be kept in mind, however that other abnormalities may also occasionally prolong clotting and they should be excluded They are a decrease (fibrinogenopenia) or absence of fibrin (afibrinogenemia) a deficiency of prothrombin accelerators or the presence of a circulating anticoagulant

The method of Quick (43) is the one most commonly used in clinical medicine There is no question but what this one stage procedure is satisfactory in meeting the needs of the clinician It is true that when there is a deficiency in the labile factor the test measures the deficiency of prothrombin and also the labile factor According to Quick (43) this source of error may be eliminated by mixing three parts of deprothrombinized rabbit plasma with seven parts of the plasma to be tested By such a procedure the labile factor is restored and it is then possible to make a fairly reliable estimate of the prothrombin content of the plasma According to Quick the test is inaccurate only in the occasional case in which there is a congenital or acquired decrease in the labile factor and in the presence of heparinemia or afibrinogenemia It should be kept in mind however that any type of circulating anticoagulant in the blood which is an exceedingly rare condition may likewise cause an apparent lengthening of the prothrombin time as determined by this method

The two stage method (44) of estimating prothrombin is too intricate and time consuming for routine clinical use The principle of the method is as follows the prothrombin in defibrinated plasma is first converted

to thrombin the latter is then estimated by determining the highest dilution of the defibrinated plasma which will cause clotting of a standard fibrinogen solution in a definite interval of time The amount of *prothrombin present is expressed in units one unit* being equal to the amount necessary to form one unit of thrombin The latter is determined by noting the amount of thrombin necessary to cause clotting of 1 cc of fibrinogen solution in 15 seconds under standard conditions The amount which is normal for human plasma is given as 300 *units which is considered as 100 per cent (45) When it was discovered* that Factor V deficiency would introduce an error a modification of the test was introduced (*46*) which consisted of supplying Ac globulin in the form of dilute beef serum It is possible to determine the amount of Ac globulin which is present by comparing the original and modified two-stage method (*46*) A quantitative method of determining the amount of plasma accelerator globulin has also been devised (*47*)

It is the opinion of Biggs (*48*) that the one stage prothrombin determination is useful as a guide to the administration of dicumarol therapy as an aid in the investigation of vitamin K deficiency In her opinion it provides a rough quantitative measure of a coagulation defect which may result from prothrombin or factor V deficiency or to an abnormality in the thrombin fibrinogen reaction She believes that the two-stage test furnishes a method for distinguishing between factor V and prothrombin deficiencies but there is no exact quantitative measure of these two substances at present

An extensive discussion and evaluation of the methods of determining prothrombin is given in the *Third Conference Relating to Blood Clotting and Allied Problems* Josiah Macy Jr Foundation published in 1950 (*49*)

The Prothrombin Consumption Test —This test which was introduced in 1949 by Quick and Favre Gilly (*50*) is based on the principle that a determination of the prothrombin in the plasma before clotting and in the serum after coagulation is complete will indicate the amount of prothrombin which is consumed in the process There is a difference of opinion as to the reliability of the technic employed in the performance of the tests used in the estimation of prothrombin As stated by Alexander Landwehr and Addleson (*51*) the accuracy of the determinations depends on the specificity of methods for measuring prothrombin concentration in the plasma and serum

It has been determined that in a great majority of conditions associated with defective coagulation of the blood there will be a high residual of prothrombin after the clotting process has proceeded to its maximum limits This is because there is usually a disturbance in thromboplastin conversion to thrombin or a retardation in the formation of thromboplastin Hence in hemophilia thrombocytopenia thrombasthenia Ac globulin deficiency hyperheparinemia and other hemorrhagic conditions associated with circulating anticoagulants prothrombin consumption is

less than normal and residual serum prothrombin is abnormally high (51) In hypoprothrombinemia however, as the original concentration in the plasma is low there will be no indication that the prothrombin consumption as shown by this test is high

The greatest value of a positive prothrombin consumption test is that it serves as evidence of some type of defective blood coagulation in any given patient In normal individuals it has been observed that about 20 per cent of the prothrombin remains in the serum after coagulation is complete (52 53) In hemophilia and in thrombocytopenic purpura however there is a pronounced diminution in the consumption of prothrombin as the residual one hour after complete clotting is often more than 70 per cent (52 50 54) The accuracy of the one stage technic is questioned on the grounds that the estimation of prothrombin by this method shows more prothrombin in the serum than in the plasma This has been attributed to the formation of serum prothrombin conversion accelerator ("SPCA"), a serum accelerator In the two stage method the accelerator is inactive and the total amount of prothrombin is measured instead of the speed of the reaction According to Langdell Graham and Brinkhous (55) the addition of "SPCA" in the one stage technic would avoid the discrepancy between the two methods It is their belief that the two-stage system of measuring prothrombin is more accurate than the one stage method, since in the former the plasma prothrombin conversion factors which may be evolved in the clotting process are not measured as they are in the one stage technic

Discovery, Isolation, Synthesis and Relation of Vitamin K to Prothrombin—The earliest observation that a dietary factor other than vitamin C is related to a hemorrhagic state and therefore to the normal clotting process was made by Henrik Dam of Copenhagen in 1929 (56) He noted as an incidental observation in a study of the cholesterol metabolism of chicks that when they were fed a synthetic diet a hemorrhagic condition appeared which could not be prevented or cured by citrus juice The same tendency to bleed was observed by McFarlane Graham and Richardson in 1931 (57) in chicks which had been fed a diet consisting exclusively of fish meal which had been extracted with ether They also made two additional observations of importance namely 1 that vegetable proteins prevented the condition whereas cod liver oil did not and 2 that the blood in chicks with this condition failed to clot Further studies which were made by Holst and Halbrook (58) demonstrated that the bleeding disorder could be cured by the administration of cabbage Hence they concluded erroneously despite previous evidence to the contrary that the abnormal bleeding was due to a vitamin C deficiency In 1934 Dam and Schonheyder (59) in a paper entitled "A Deficiency Disease in Chicks Resembling Scurvy" reported that certain cereals had a preventive and curative action Schon

heyder in 1935 (60) noted as had McFarlane and his associates in 1931 that there was a prolonged coagulation time in the experimentally induced state In the same year Dam (61) came to the conclusion that the deficiency was due to some unidentified substance which he termed "vitamin K or the "Koagulation vitamin Shortly thereafter Almquist and Stokstad (62) confirmed the work of Dam and discovered for the first time that the vitamin could be formed by putrefaction of fish meal It was Halbrook (63) in 1935 who observed initially that if 5 per cent of dehydrated alfalfa or an equivalent amount of the ether extract of the material were added to the diet it prevented the appearance of the abnormal tendency to bleed

Credit for the discovery of the important relation of vitamin K to prothrombin must be accorded Dam Schonheyder and Tage Hansen (64) who in 1936 found that this component of the normal clotting process could not be formed in the blood of chicks in which there was a vitamin K deficiency These observations were confirmed and extended by Quick (65) in 1937 who observed 1 that the prothrombin rapidly decreased in chicks given a vitamin K free diet 2 that the bleeding tendency appeared when the prothrombin dropped to about 10 per cent of normal and 3 that when alfalfa was added to the diet it promptly and effectively restored the prothrombin level of the blood *Hence these observations definitely established the relationship between the prothrombin of the blood and vitamin K Furthermore they demonstrated that bleeding did not occur until the prothrombin had diminished to about 90 per cent below normal*

The Chemical Composition of Vitamin K —Vitamin K_1 as first prepared by Dam Karrer and co workers (66) is a fat soluble pale yellow oil which was found to contain carbon hydrogen and oxygen Doisy and his associates (67 68) were the first to show that both K_1 and K were derived from 1 4 naphthoquinone and K obtained from putrefied fish meal was probably 2 methyl 3 difarnesyl 1 4 naphthoquinone The two substances have a very close relationship to each other in chemical structure for they have the same quinone nucleus and each possesses a long side chain

Having gained information concerning the structure of the natural vitamins study was directed toward the various naphthoquinone derivatives It was soon established that the simple compound 2 methyl 1 4 naphthoquinone now officially designated as menadione by the Council on Pharmacy and Chemistry of the American Medical Association had a high vitamin K activity As Fieser says (69) with reference to this chemical " the simple substance is found by the chick assay method to be about three times as potent as vitamin K_1 at least on a weight basis It is possible that Nature for once has been outdone and that a simple substance obtained merely by oxidizing one of the hydrocarbons found in coal tar is per se superior in potency to a vitamin factor produced by

plant synthesis and provided with the elaborate phytyl chain derived from chlorophyll

Natural Distribution of Vitamin K.—It is now established that vitamin K is not present in large amounts in the animal body which indicates that little of it is stored. The livers of fish, rats and young chicks contain a low concentration of the vitamin but there is more in swine liver. There is only a small amount in milk although probably this is ordinarily sufficient to meet the demands of the newborn. The vitamin is distributed widely in the green leaves of plants and is especially abundant in alfalfa, chestnut leaves and spinach. Cereals, beans, peas, carrots, potatoes and most fruits are poor sources. It is apparently true that the amount of vitamin K present in foods that grow in the dark is small except in the coniferae which can also form chlorophyll without light. According to Damm (66) vitamin K is a product of the chloroplasts. Yeast does not contain vitamin K.

It is of great interest to note that the vitamin is synthesized by bacteria, an observation which was first made by Almquist and Stokstad and later studied in more detail by Almquist and his collaborators (70, 71). It has now been established that E. coli, the tubercle bacillus and other common bacteria have the power to synthesize the vitamin but apparently it is not liberated and made available for use until the organisms disintegrate. This is a possible explanation of why rats do not develop a deficiency when they are placed on a diet lacking in vitamin K for it is formed in abundance in the large intestine by the normal flora found there. On the other hand, chicks do not have such a resistance because their large intestine is short as compared with rats and consequently in the former this source of vitamin is unimportant.

An observation of considerable significance possibly relating to the synthesis of vitamin K in the intestinal tract of rats has been made by Black and his collaborators (72). These observers found that the addition of sulfaguanidine or succinylsulfathiazole to a synthetic ration is followed by a state of hypoprothrombinemia in young rats. It is assumed that the drug either inhibits the synthesis of vitamin K by reducing the intestinal flora or as it has been shown clinically that the sulfonamide drugs may cause liver damage this may also play a role in the hypoprothrombinemia. They found that liver extract or vitamin K counteracts the prothrombin effect.

The Relation of Vitamin K Deficiency to Abnormal Bleeding.—In resume it may be said that our present knowledge concerning the physiology of vitamin K is as follows. Vitamin K is a component of the normal diet being present largely in green leaves and it also may be synthesized by the bacteria which are normally present in the intestinal tract. Bile favors absorption but it can occur to some extent in the absence of bile. Upon being absorbed it is carried by the portal vein to the liver where it

is in some as yet unknown way concerned with the formation of prothrombin If for some reason there is a reduction in the amount of vitamin K which is available or a disturbance in the liver which is vitally concerned with the relation between the vitamin and prothrombin then the amount of the latter in the blood will decrease and a tendency to bleed may develop

From a theoretical standpoint therefore a diminished amount of prothrombin and therefore a prolonged prothrombin time might result from the following

1 Due to dietary defects in adults and in infants (hemorrhagic disease of the new born)

2 Faulty absorption of vitamin K in patients with jaundice and bile fistulae in sprue chronic ulcerative colitis the dysenteries etc

3 Impaired formation of prothrombin by the liver as might be observed in cirrhosis of the liver Banti s syndrome acute yellow atrophy injury to the liver by various chemicals and other conditions

4 Idiopathic hypoprothrombinemia

5 Inactivation of prothrombin by dicoumarin and heparin

Type of Bleeding and Diagnosis of Hypothrombinemia —Regardless of the cause the type of bleeding in hypoprothrombinemia is the same Spontaneous bleeding does not occur unless the prothrombin concentration is below 8 to 10 per cent Hemorrhage may occur into the skin the genitourinary gastrointestinal and respiratory tracts It is not common however for the hypoprothrombinemia to proceed to such a stage that spontaneous bleeding appears It is usually observed when there is some other contributing factor present such as ulceration of the intestinal tract or following surgical operations In a patient with dicumarol poisoning described elsewhere (see page 568) Duff and Shull (73) report that the patient was bleeding spontaneously into the skin from the respiratory tract as shown by blood streaked sputum from the mouth vagina and urinary tract as indicated by a gross hematuria The clotting time in this patient was 48 minutes the bleeding time was seven minutes and the prothrombin time by the Quick procedure as prolonged to 500 seconds on one determination and 800 on another with a control time of 16 seconds It was not possible to estimate the prothrombin concentration from the standard dilution curve as the prothrombin was so depleted

Deficiency of Prothrombin Due to Dietary Defects —It has been established that vitamin K deficiency does not occur commonly in mammals even though the vitamin is completely eliminated from the diet This may be mainly because the material is synthesized by the bacteria in the intestinal tract which can ordinarily supply a sufficient quantity to meet the needs of the body In addition as the vitamin is fairly well distributed in the dietary of the average individual at least in this

country it is unlikely that the food intake for any long period of time would be deficient in the vitamin K intake In rats however despite the fact that the flora of the intestinal tract can synthesize the substance, it is occasionally possible to produce a vitamin K deficiency by eliminating this vitamin from the food intake (74) Furthermore it has been demonstrated that although active evidences of a vitamin K deficiency may not be apparent in mammals when the vitamin K intake is restricted, it is known that the reserves of this vitamin in the body may be depleted (74 75)

The report of Kark and Lozner (76) is of great interest because they have observed four persons with nutritional deficiency in which the moderate prolongation of Quick s prothrombin time was corrected by the administration of vitamin K From these observations they suggested that at least a moderate deficiency of vitamin K may be observed in persons who partake of an inadequate diet over a long period of time

Studies bearing on this made by Warner Spies and Owen (77) indicate that a vitamin K deficiency may occur occasionally in patients with pellagra In addition, they concluded that many chronic debilitated persons have a moderate hypoprothrombinemia which is apparently due to other causes than a vitamin K deficiency They observed the plasma prothrombin levels in 48 patients seen at the Hillman Hospital Birmingham, Alabama in whom there was clinical evidence of a deficiency of one or more of the factors of the vitamin B complex and compared them with a series of patients studied at the University of Iowa in which there was essentially the same age distribution The latter group gave no evidence of a vitamin deficiency and were suffering for the most part from arthritis and diabetes mellitus These observers found in the 48 patients with nutritional deficiency all but six had prothrombin values above 80 per cent of normal and in only one patient was it below 60 per cent Actually they noted that the incidence of definite hypoprothrombinemia was greater in the control group of patients studied at the University of Iowa who did not have evidence of a vitamin deficiency In this group 10 of the 37 patients had values below 80 per cent but none were below 60 per cent

If the hypoprothrombinemia were due to a deficiency of vitamin K it would be expected that the administration of a potent vitamin K preparation would at once cause a rise in the prothrombin of the blood In order to test this [illegible] milligrams of synthetic vitamin K (2 methyl 1 4 naphthoquinone dissolved in corn oil) was given orally to five of the six patients in the nutritional deficiency group and to eight of the 10 patients in the other series Bile salts were given with the vitamin to insure complete absorption It is interesting to note that only two of the five patients in the nutritional deficiency group responded which was an indication that in the two only was there a hypoprothrombinemia due to a deficiency of vitamin K One of these patients was a 78 year old white male who had

suffered from recurrent attacks of pellagra for many years The prothrombin value in this patient's blood was only 33 per cent of normal and there was gross blood in the stools There were no pathological changes in the gastrointestinal tract which could account for this that could be demonstrated by the roentgen ray Following the administration of vitamin K therapy for a period of five days the prothrombin rose to 69 per cent and the bleeding ceased The second patient had an initial reading of 69 per cent of prothrombin which rose to 96 per cent after three days of vitamin K therapy

The remaining three patients in this series and the eight patients of the control group failed to show any response to this form of therapy It should be concluded in the case of these patients therefore that whatever might have been the cause of the hypoprothrombinemia it was not due to a deficiency of vitamin K

It was pointed out by Warner and his associates (77) that in both of the patients with the nutritional deficiency who showed a response to vitamin therapy there was a history of a prolonged and severe diarrhea It seems likely therefore that this rather than a deficient diet *per se* was responsible for the vitamin deficiency

Of considerable interest is the presence of the moderate hypoprothrombinemia (65 to 85 per cent of normal) in a number of the patients in both series That it is not due to a deficiency of vitamin K is demonstrated by the fact that the prothrombin does not increase following the administration of vitamin K in an adequate therapeutic dosage The authors state that one might hypothesize subnormal prothrombin formation as a result of general debility but also comment that a better understanding of the formation and utilization of prothrombin in the future will perhaps make possible the elucidation of this problem

In summary then it would not seem likely that a decrease of prothrombin results from a deficiency of vitamin K in the diet On the other hand a deficient diet may produce diarrhea as is observed in pellagra and this in turn may lead to impaired absorption of vitamin K and a lowering of the prothrombin level of the circulating blood

HEMORRHAGIC DISEASE OF THE NEWBORN

Synonyms —Morbus haemorrhagica neonatorum melena neonatorum hemorrhagic diathesis of the newborn hemophilia neonatorum

Definition —This condition may be defined as a specific disease entity associated with a hypoprothrombinemia which usually manifests itself clinically in the first week of life in the form of spontaneous hemorrhages These may occur in any tissue of the body but especially the skin and subcutaneous tissues the umbilical stump and the intestines The cure is accomplished promptly by the administration of vitamin K or allied substances orally or parenterally

It should be emphasized however, as Kugelmass (78) has stated *that not all hemorrhagic manifestations in the newborn are due to acute hypoprothrombinemia, and therefore should not be included as examples of hemorrhagic disease of the newborn* Bleeding in the newborn therefore, may be due to an abnormal clotting mechanism which results from a number of conditions It may be associated with a decrease in platelets causing a thrombopenic purpura there may be a condition known as thrombopathy which some attribute to an altered function of the platelets the defect may be in rare instances one of a deficient fibrinogen or there may be bleeding with purpura due to increased capillary permeability on a basis of allergy infection or toxemia, and finally both the clotting mechanism and the capillaries may be normal and yet there be bleeding due to a vascular accident incident to the birth process Maloney (79) found a low capillary resistance in over one half of the newborn infants which he suggests may have a relationship to abnormal bleeding in the newborn

In the past hemorrhagic disease of the newborn has been regarded as one due to any defect in the clotting mechanism thereby excluding vascular injury The present day view is that the disorder is one associated solely with a prothrombin deficiency A failure to adhere rigidly to this concept has caused a considerable amount of misunderstanding and difference of opinion about the cause and treatment of the condition If all will agree to the definition as given above these differences can now be more readily reconciled

Etiology —Hemorrhagic disease of the newborn due to hypoprothrombinemia is present in about 0 5 per cent of all infants within a few days after birth If all types of bleeding which occur in the first few days of life are included the incidence is about 6 per cent (80) Hypoprothrombinemia with bleeding occurs with the same frequency in both sexes and all races It is always present within the first 10 days of life and usually the first week The cause of this condition remained obscure for many years In 1913 Schloss (81) summarized what he considered to be the main causes of this condition and mentioned hemophilia infection congenital lues gastric and duodenal ulcers defective coagulation lack of fibrinogen prothrombin and localized vascular lesions Schwarz and Ottenberg in 1910 (82) had observed uncontrolled hemorrhage in this condition and attributed it to some disturbance in thrombokinase (thromboplastin) It was the work of Whipple in 1912 (83) which very definitely established that there was a decrease of prothrombin in a case of melena neonatorum but for some unknown reason this highly important and valuable information was overlooked for a period of years

In 1920 Rodda (84) observed that the clotting time of infants blood was prolonged within a few days after birth with a maximum on the fifth day after which it gradually returned to normal on the tenth day It is

now known that this change in the coagulation time can be directly correlated with the alterations in the amount of prothrombin present in the circulating blood This was discovered in 1937 by Brinkhous Smith and Warner (85) who observed that the prothrombin time in newborn infants with abnormal bleeding was greatly increased and hence they concluded correctly that the hemorrhage was associated with a hypoprothrombinemia They did not mention however the possibility that the latter condition was associated with a deficiency of vitamin K According to Quick (86) Dam Hygaard and Quick all three independently came to the conclusion that this physiological hypoprothrombinemia was due to a

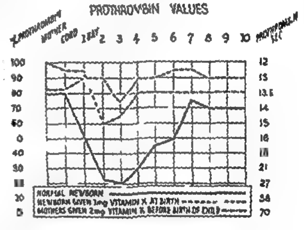

Fig 51 —This diagram shows the normal prothrombin values during the first ten days of life as compared with those receiving vitamin K at birth and in those born of mothers who had been given vitamin K before the birth of the child During the newborn period the plasma prothrombin diminished during the first second and third day of life and increased during the fourth fifth and sixth days of life and almost returned to cord value from the seventh day throughout the newborn period The amount of the plasma prothrombin could be increased above the plasma prothrombin level by the administration of vitamin K to the infant The plasma prothrombin of the mother and the cord plasma prothrombin of her infant could both be increased above normal values by the administration of vitamin K to the mother before the birth of her child The plasma prothrombin values of infants given vitamin K or given to their mothers before delivery is well above that of normal infants throughout the newborn period (Sanford Shmigelsky and Chapin courtesy *Journal of the American Medical Association*)

dietary lack of vitamin K and that it was not until the intestinal flora were established and hence producing vitamin K that there was a restoration of the prothrombin level in the newborn infant This theory though plausible still is lacking in experimental proof although all concede that the hypoprothrombinemia is due to a deficiency of vitamin K

The present view which has been tentatively accepted by many but is still lacking in complete proof may be stated as follows At birth the infant presumably lacks a sufficient reserve of vitamin K to restore at once the prothrombin which is lost in the first few days following birth Apparently the infant under ordinary circumstances cannot store a sufficient supply to prevent the prothrombin from decreasing considerably during the first few days of extrauterine life This may be prevented however

by administering vitamin K to the mother in the last week of pregnancy and continuing the dosage until the very onset of labor

The changes in the prothrombin percentage and the prothrombin time in infants in the first 10 days of life are shown in the chart prepared by Sanford, Shmigelsky, and Chapin (80) from observations on many newborn infants From this chart, it will be seen that the prothrombin falls from a level of 80 per cent at birth to 20 per cent of normal which is perilously close to the point of abnormal hemorrhage The curve rises spontaneously on the fourth day and by the seventh day it has returned approximately to normal This curve also shows, very convincingly that the administration of vitamin K to the infants at birth or to the mothers shortly before the birth of the child will prevent the drop in the percentage of prothrombin in the blood One possible cause of a pathological hypoprothrombinemia therefore is the absence of adequate stores of vitamin K in the mother which is reflected in the inadequate reserves of the newborn infant If for any reason the percentage of prothrombin should fall to the level of 25 per cent of normal or less pathological hemorrhage is likely to occur

It should be remembered that certain factors in the infant may also contribute to the low level of prothrombin in the circulating blood A slight loss of blood may be one of the precipitating causes for it should be emphasized that the loss of 30 cc of blood in a newborn infant is equivalent to the loss of at least 500 cc in an adult Hence small hemorrhages in an infant may mean the loss of a sufficient amount of prothrombin to a point where active hemorrhage will occur Trauma neonatal asphyxia and impaired liver function may be factors of immediate importance In general however it may be said that the main cause of hemorrhagic disease of the newborn is a lack of an adequate store and dietary supply of vitamin K which leads to a hypoprothrombinemia Admittedly however there are other important facts concerning the etiology which are not known at present

That this view has not received complete acceptance is indicated by the title of an article written by Sanford Shmigelsky and Chapin in 1942 Is Administration of Vitamin K to the Newborn of Clinical Value?" (80) In this comprehensive study they observed that the physiological fall in the prothrombin during the first few days of life could be prevented by the administration of vitamin K either to the mother just before birth of the child or by giving it to the child Although by both of these methods of administration it was possible to increase the plasma prothrombin above the normal values this did not affect the frequency of the hemorrhagic manifestations in their patients In other words they found in their series just as many conjunctival vaginal petechial cerebral and umbilical hemorrhages and cases of melena and cephalematomas in one group as another In the untreated infants the percentage of hemorrhages was 6 6 and in the group which received vitamin K it was 6 59

This publication brought prompt protests from Quick (87) from Kugelmass (78) and from Waddell (88) in which the main point of argument was that there may be many causes of neonatal bleeding but that hypoprothrombinemia is the only one which vitamin K therapy will prevent According to Kugelmass acute hypoprothrombinemia is the only bleeding condition in the newborn which responds to vitamin K therapy It is his belief that as this disease only occurs in less than 0.5 per cent of all newborn infants it is "folly" to waste vitamin K on 99 5 per cent of the remainder He states that if the latent hemorrhagic tendency present in all newborn infants becomes active the rise in clotting time will indicate the decrease in available prothrombin When this occurs he advises that then and then only is vitamin K therapy indicated In refutation of the view held by Sanford and his associates Waddell (88) cites his group of cases treated by vitamin K in which the incidence of hemorrhage as 1 07 per cent whereas the incidence in the control group in which vitamin K was not given was 10 4 per cent

The observations by Sanford and Shmigelsky (89) on one child with congenital absence of the gallbladder and bile ducts and two other newborn infants with complete atresia of the esophagus have an important bearing on the theories regarding the absorption and bacterial synthesis of vitamin K and the formation of prothrombin One child was observed in whom bile did not enter the intestinal tract for a period of five months due to the congenital anomaly and yet the prothrombin remained at a normal level This is strong evidence that *bile is not absolutely essential* for the absorption of vitamin K from the intestines The accumulated data however indicate that while bile is not necessary it does facilitate its absorption

Of great interest also is the observation that in the two infants with atresia of the esophagus which absolutely prevented all food from entering the stomach and small intestine the plasma prothrombin remained at a normal level throughout the 14 days of life in each case In one child life was sustained by blood transfusions and subcutaneous injections of salt solutions The prothrombin determination on the fifth day (the only estimation) was 45 per cent which is about the normal level for an infant of that age This determination was made before the blood transfusions had been given

In the second child with congenital atresia of the esophagus no food or fluid was administered during the 14 days of life The plasma prothrombin determinations done on the first third fifth seventh and twelfth days of life were 50 per cent 25 per cent 59 per cent 60 per cent and 60 per cent respectively These readings are approximately the same as the estimations of prothrombin in per cent of normal which are observed in a normal newborn infant

These studies indicate therefore that the prothrombin levels of the blood approximating those observed in a normal infant may be present for

by administering vitamin K to the mother in the last week of pregnancy and continuing the dosage until the very onset of labor

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but also from circumcision or cutting the frenum of the tongue Sometimes there may be a continuous but slow loss of blood which is not controlled by ordinary measures and this may result in the production of a severe anemia of the hypochromic type

Internal bleeding is most commonly observed in the intestine and this may give rise to bloody stools a condition which for many years has been termed melena neonatorum The bleeding may be in the stomach which results in the vomiting of blood Loss of blood may also occur from the urinary tract and the vagina

Intracranial hemorrhage is the most serious complication which is encountered in this disease This may lead to death or pronounced permanent injury to the nervous system which may persist throughout life Here also it should be emphasized that all instances of intracranial hemorrhage are not due to a deficiency in prothrombin The type of cerebral hemorrhage which occurs immediately following birth is most commonly associated with trauma and injury to the blood vessels In bleeding of this nature there is no disturbance of the clotting mechanism On the other hand the cerebral bleeding which occurs from four or five days to a week after birth is in many instances associated with a prothrombin deficiency Experience has shown that this type of hemorrhage can be benefited by vitamin K therapy and there is every reason to believe that the administration of this therapeutic agent is effective as a prophylactic measure If the cerebral bleeding is due to hypoprothrombinemia it usually occurs several days following birth there is a decrease in the prothrombin content of the blood and usually the hemorrhage is not confined to the brain but is also present in other parts of the body

Diagnosis —The recognition of abnormal bleeding is of course obvious The diagnostic difficulty arises in differentiating the various types of hemorrhagic states which may occur in the newborn The condition should not be confused with the rare instances of idiopathic thrombopenic purpura which has been known to occur at birth when the mother is afflicted with the same condition The presence of the disease in the mother the remarkable decrease in the platelets of the circulating blood the prolonged bleeding time the failure of the clot to retract and the normal prothrombin time all should make this disease state an easy one to differentiate from true hemorrhagic disease of the newborn Congenital afibrinogenemia is an exceedingly rare condition but should be suspected when there is a complete absence of coagulation of the blood In some instances allergy to cow s milk may be responsible for intestinal bleeding (92) but this condition does not arise until the infant is several weeks of age Ordinarily hemophilia does not make its appearance before the end of the first year and therefore is not likely to be confused with hemorrhagic disease of the newborn

Treatment —Vitamin K preparations may be employed prophylactically by administration to the mother before the onset of labor, or to the

short intervals in infants in whom congenital anomalies prevent the presence of food or bile in the gastro intestinal tract Further observations are desirable to affirm these most important studies It is doubtless true that vitamin K may be absorbed from the intestines in the absence of bile as the latter only facilitates the absorption Furthermore perhaps in some infants the store of vitamin K or prothrombin in the liver is adequate to provide a sufficient quantity of prothrombin in order to maintain it at a normal level in the blood for a period of at least two weeks

It is obvious that some observers consider additional time and more extended observations are necessary to establish the exact relationship of vitamin K and hypoprothrombinemia to hemorrhagic disease of the newborn Nevertheless it must be admitted that recent investigators have shed a great deal of new light on the subject At the eleventh annual meeting of the American Academy of Pediatrics held in Boston October 9 to 11 1951 a round table discussion on Hemorrhage in the Newborn was held in which all of the aspects of this question were discussed At this conference in a summary of his views on the subject Waddell (90) made the following statements which are quoted verbatim Certain facts concerning hemorrhagic disease of the newborn which in the past have been unexplained now seem quite clear 1 that hypoprothrombinemia is the immediate cause of prolonged clotting time can no longer be questioned 2 the fact that marked prothrombin deficiency is usually corrected by the fifth day is striking evidence of etiological relationship to hemorrhagic disease 3 the seasonal incidence of hemorrhagic disease which has received scant notice in the older literature assumes new importance and would seem adequately explained by an identical seasonal incidency of hypoprothrombinemia 4 hypoprothrombinemia and associated prolonged clotting are efficiently prevented by administration of vitamin K 5 hemorrhage associated with hypoprothrombinemia and prolonged clotting time is promptly controlled by administration of vitamin K and 6 recent data confirm the suggestion that hemorrhagic disease with prolonged clotting time will not occur in any infant adequately treated in a prophylactic fashion In support of this statement Dr Waddell submits data indicating that in 4141 newborn infants treated prophylactically with vitamin K there had not been a single incidence of hemorrhagic disease On the other hand Potter (91) administered vitamin K to over 6000 women prior to delivery and compared the incidence of stillbirths and deaths of infants with an untreated group There was practically no difference in mortality

Clinical Manifestations—Evidence of the disease rarely appears before the fourth day or after the tenth day following birth The onset of the bleeding is with a slow oozing commonly from the stump of the umbilical cord or into the skin which usually results in large ecchymotic areas Petechiae are characteristically absent In some instances the abnormal bleeding may be initiated by trauma especially from forceps

the cause of abnormal bleeding due to jaundice It is interesting to note that this same observer determined in 1912 (83) that there was a decrease in the prothrombin of the blood in patients with hemorrhagic disease of the newborn In both instances this highly important and correct observation was not appreciated for a long period of years

In 1932 Quick having developed a new method for the estimation of prothrombin made the important observation that this component of the clotting process was greatly decreased in certain patients with obstructive jaundice and hence the work of Whipple which had been done 19 years before was confirmed

It is now known that the most important cause of hypoprothrombinemia in the adult is obstructive jaundice Such a condition is thought to arise in jaundiced patients largely because there is a lack of bile salts in the intestine which prevents the absorption of the fat soluble K in amounts sufficient to meet the normal demands of the body It is recognized that not all patients with obstructive jaundice have a hypoprothrombinemia which reaches the point at which bleeding occurs According to Quick (96) abnormal bleeding is not likely to be present until the prothrombin is reduced to below one fifth of normal Goldstein and Alexander (97), however state that bleeding does not usually occur unless the prothrombin concentration is reduced below 7 per cent of normal unless other defects in the hemostatic mechanism exist

The following data taken from Quick (96) show the relationship between the clotting time in seconds and the reduction in the prothrombin expressed in per cent of normal

Clotting Time (in seconds)	*Prothrombin (per cent of normal)*
12	100
12 ½	80
13 ½	60
15	50
17	40
19	30
25	20
38	10

From this table it is apparent that an unduly prolonged clotting time of 25 seconds is obtained when the prothrombin is reduced to the critical level of 20 per cent of normal Hence it is obvious that normally there is an excess of prothrombin in the blood which serves as reserve Dangerous bleeding does not occur therefore until there is a striking reduction in the total amount of circulating prothrombin Although postoperative bleeding commonly occurs when there is a severe hypoprothrombinemia due to common duct obstruction or a biliary fistula it is unusual for a purpuric type of hemorrhage to be observed in association with these conditions According to Quick (4) when it does occur one should suspect that some additional cause as a thrombocytopenic purpura is present in addition to the hypoprothrombinemia

infant at birth or both The results of such a plan are in dispute According to Potter (91) and to Hay Hudson and Rodgers (93) this prophylactic procedure has no particular advantage On the other hand the oral administration of 2 0 milligrams daily of menadione for one week prior to delivery to the mother can do no harm Or the mother may be given 2 5 milligrams of menadione sodium bisulfite intramuscularly daily for two days before delivery and the infant 1.5 milligrams at birth

If a hemorrhagic condition is present in the newborn infant and it is associated with a hypoprothrombinemia then synthetic vitamin K, menadione (2 methyl 1 4 naphthaquinone) 1 0 milligram, may be administered intravenously, intramuscularly, or orally and repeated every six hours until the prothrombin level is normal With this medication the prothrombin time is usually decreased within two to six hours and the bleeding is controlled

Entire dependency should not be placed however on vitamin K preparations alone in this condition as transfusions of fresh whole blood have even greater value in controlling the bleeding and also make up for the loss of blood Transfusions should be given on the basis of 8 to 10 cc per pound of body weight

THE ASSOCIATION OF JAUNDICE AND A HEMORRHAGIC STATE

For many years although the cause was unknown, it has been recognized that patients who were jaundiced had an abnormal tendency to bleed In 1891 Osler in the first edition of his textbook makes the statement that ecchymoses are not uncommon in severe jaundice particularly in the more malignant forms In 1901 he also warns that surgeons must take into consideration the liability to bleeding in chronic jaundice Well do I remember the experience which I had as an intern when the ear of a deeply jaundiced patient was pricked in order to obtain blood for the necessary blood counts For hours thereafter there was a steady slow dripping of blood from this minor wound and an enormous ecchymotic area developed at the bend of the elbow following removal of blood for the Wassermann test The surgeons for years have regarded excessive hemorrhage as one of the major hazards of biliary surgery According to the estimate of Butt and Snell (94), it was responsible for an added risk of about 5 per cent in surgery involving the biliary tract

For many years the cause of the bleeding associated with jaundice was unknown although many theories were suggested Among these was the theory that there was a deficiency of fibrinogen and also that the calcium was less than normal Some thought that the bile pigments and salts were at fault (95) and it was proposed by others that the sulfur amino acids played an important role in this connection In 1913 Whipple for the first time made the correct observation that a deficiency of prothrombin was

plasma bank blood or plasma or dried plasma with satisfactory results as prothrombin is relatively stable They state that the transfusion of 500 cc of blood will raise the prothrombin from 5 per cent to about 12 per cent which in their opinion is a level for adequate hemostasis if other factors are normal It should be emphasized however that the infused prothrombin disappears rapidly from the circulation (*100*) and hence a repetition of blood and plasma transfusions is necessary every three or four hours to prevent hemorrhage if dependence is placed on this type of therapy alone

It has been reported by Kinsey (*101*) that patients with a hypoprothrombinemia associated with liver disease could be treated more successfully by transfusions of blood fortified by the administration of vitamin K to donors A study by Butt and his associates (*102*) however failed to confirm this claim and furthermore they did not observe that the hypoprothrombinemia secondary to obstructive jaundice was benefited by this procedure

In my opinion in such cases regardless of the use of blood transfusions *vitamin K therapy should be instituted at once* If the liver has not suffered too much damage secondary to prolonged biliary obstruction or for other reasons this medication should result in a satisfactory return of the plasma prothrombin to a higher level within 24 hours This therapy in my opinion should be given in the form of a soluble intravenous preparation such as menadione sodium bisulfite (Hykinone) or Synkamine The standard dose of both preparations is given as 5 milligrams It has been our practice however at the University of Michigan Hospital to give as much as 72 milligrams of Hykinone intravenously as a single dose from which no untoward effects have been noted and satisfactory results have been attained Usually one dose suffices to raise the prothrombin concentration to a satisfactory level If not the same dose is repeated every 24 hours with or without blood transfusions depending on circumstances until the proper level is reached More recently Gamble and his associates at the University of Michigan (personal communication) have confirmed the observation that the oil soluble vitamin K_1 (mephyton) in doses of 50 milligrams intravenously is much more effective than menadione sodium bisulfite

As there may be some loss of blood during the operation a blood transfusion should be given during the surgical procedure if necessary and postoperatively as indicated It may also be advisable to give 72 milligrams of Hykinone intravenously every day postoperatively for several days

Hypoprothrombinemia in Association with Biliary Fistula—This condition is of interest because it demonstrated the necessity of the presence of bile in the digestive tract in order for the normal absorption of vitamin K to take place The fact that an abnormal tendency to bleed occurs in

Before the advent of vitamin K, hemorrhage was the cause of death in approximately 50 per cent of the cases of obstructive jaundice in which patients died following surgical intervention In contrast to these findings Anddrus and Lord report (98) that since the use of vitamin K there has not been a single death due to hemorrhagic tendency in patients with obstructive jaundice of extrahepatic origin on the surgical service of the New York Hospital In their opinion it is not wise to perform an elective operation on any patient with a level of plasma prothrombin below 50 per cent as the critical bleeding level is 20 to 25 per cent by the Warner Brinkhous and Smith test Hence allowing 25 per cent for the postoperative fall, there would be no margin of safety unless the plasma prothrombin were 50 per cent or higher preoperatively

It is now generally agreed that surgery should not be attempted in these patients if the prothrombin level is below 50 to 60 per cent Usually unless some complication is present as previously stated, the bleeding is not apparent until surgery is attempted The reasons for its appearance then are thought to be the following there is some loss of blood occasioned by the operation which means a further loss of prothrombin the semi fasting period immediately prior to the operation may deplete the stores of vitamin K in the body there may be transient hepatic damage from the anesthesia and hence the transformation of vitamin K to prothrombin is hampered or the surgical trauma and anoxemia may in some unknown manner interfere with the utilization of vitamin K

When bleeding does occur in patients with jaundice following operation it is most frequently in the form of a slow oozing from the abdominal wound but it may be internal It is reported by Petren (99) that about one third of the cases bleed from the surgical incision one third bleed intra abdominally and the remainder have hemorrhage from the gastro intestinal tract

Treatment of Hypoprothrombinemia Due to Obstructive Jaundice — In the days before the discovery of the relationship between vitamin K and bleeding in jaundiced patients the treatment of the condition was highly unsatisfactory The most successful form of therapy at that time was the transfusion of blood which supplied some prothrombin but its effect was usually only transient as the prothrombin thus provided was soon exhausted Since 1938 when the striking effects of the administration of vitamin K were first demonstrated in these cases this form of therapy has been recognized as the treatment which is most rational and effective

Never should a patient with obstructive jaundice or a biliary fistula be operated upon until every effort has been made to bring the prothrombin concentration to 50 per cent or preferably to 60 or 70 per cent of normal If the concentration is below 50 per cent and the condition is acute then a blood or plasma transfusion of 250 to 500 cc should be given According to Goldstein and Alexander (97) one can employ fresh blood or

Occasionally a patient with sprue is observed to have both hemoptyses and hematuria which are due to vitamin K deficiency and hypoprothrombinemia. The prothrombin time of the circulating blood of one patient was found to be 41 seconds (*108*) whereas the normal control was 15 seconds. Prompt recovery from the bleeding tendency followed the intravenous injection of methyl naphthohydroquinone sodium sulfonate, 4 milligrams daily. The hypoprothrombinemia was attributed to the failure of absorption of the fat soluble vitamin K in a patient with steatorrhea, and also to the fact that probably bacterial synthesis of the vitamin was impaired as a result of the administration of sulfasuxadine which is known to reduce the number of bacteria in the intestinal tract.

The prothrombin content of the blood in 30 cases of sprue was studied by Rivera Suarez and Morales (*109*). In 19 or 63.3 per cent of the cases the content of the blood was estimated to be less than 80 per cent of normal. In only nine cases, however, was the prothrombin time considered to be in the danger zone of hemorrhage; in three of these (10%) the clotting activity was below 30 per cent, and in 6 (20%) it was between 61 and 70 per cent. Despite the prolonged prothrombin time and the reduced clotting activity in 30 per cent of the cases, no gross hemorrhagic tendencies were observed in this particular group. In a very limited experience (six cases) the authors conclude that the prothrombin time may be shortened by adequate liver therapy. After their preliminary study the prothrombin time was studied in six severe cases of sprue. The prothrombin content of the blood varied between 50 and 74 per cent of normal. Five of the cases were in the danger zone of hemorrhage with variations from 50 to 64 per cent less than normal. The authors state that the hypoprothrombinemia can be explained in sprue on the basis of an edematous and malfunctioning intestinal mucosa which renders absorption very difficult. This is also the explanation for the flat glucose tolerance curve which is observed in these patients when glucose is given by mouth.

The Relation of Liver Injury to Hypoprothrombinemia.—It has been established that injury to the liver may result in a hypoprothrombinemia of clinical importance. This was first demonstrated by Smith and his collaborators (*110*) in 1937. These investigators observed that there was a fall in the prothrombin of the blood in dogs following extensive injury to the liver by chloroform poisoning. Hence it became apparent from these experiments that the liver was responsible for the utilization of vitamin K in the synthesis of prothrombin. The clinical significance of this was pointed out by Butt, Snell and Osterberg (*111*) and by Quick (*112*). The latter made the following comment in 1938: "The ease with which the prothrombin of the blood can be reduced by hepatotoxic substances such as chloroform or carbon tetrachloride makes it highly probable that in a certain number of cases of jaundice the hemorrhagic tendency is secondary to damage of the liver.

animals in which a bile fistula has been produced was first observed by Hawkins and Whipple (*103*) in 1935 Here again the work of Whipple and his collaborators supplied fundamental information concerning the relation of prothrombin to bleeding as it had in hemorrhagic disease of the newborn and in the bleeding associated with jaundice The following year Hawkins and Brinkhous (*104*) reported that the abnormal bleeding was due to a deficiency of prothrombin Shortly thereafter it was demonstrated (*105*) that the diminished prothrombin of the blood associated with a biliary fistula in rats and dogs (*106*) could be restored by the feeding of vitamin K and the administration of bile orally

The first classical observations bearing on this in humans were made by Zuckerman, Kogut Jocobi and Cohen (*107*) on a subject with an external biliary fistula who was placed on a low fat and vitamin K deficient diet They noted that the prothrombin content of the blood fell to a low level and a bleeding state developed In the treatment of this condition they gave vitamin K alone and then bile orally but without effect When the two were administered simultaneously however there was a prompt rise in the prothrombin of the blood and a cessation of the bleeding These observations demonstrated clearly that a deficiency of prothrombin can arise in the human when there is an absence of bile from the intestinal tract, and that vitamin K and bile when given orally are more effective than when vitamin K or bile is given alone

Hypoprothrombinemia Due to Intestinal Disorders—Although vitamin K in the food and that synthesized by the normal flora of the intestines are ordinarily considered to provide an adequate supply it is not always absorbed in normal amounts even when an adequate amount of bile is present in the gastro intestinal tract This is because absorption depends not only upon the supply in the intestinal tract but also upon the interval allowed for it Therefore a hypoprothrombinemia may result due to short circuiting operations in which the stomach or small intestine is anastomosed to the colon or because the intestinal contents pass through the normal intestinal tract more rapidly as the result of diarrheal states

Other factors must also be considered For example it is not surprising that hypoprothrombinemia is present in sprue because in this condition there is a malabsorption of fat and fat soluble vitamins including vitamin K Furthermore if this vitamin is synthesized by the normal intestinal flora then when certain sulfonamide drugs, such as sulfaguanidine and sulfasuxadine which destroy the bacteria of the intestinal tract are given it is possible that there may be a decrease in the formation of vitamin K and a resultant hypoprothrombinemia

A hypoprothrombinemia due to malabsorption from the intestinal tract has been found in sprue intestinal polyposis ulcerative colitis intestinal fistula postoperative gastric retention gastrocolic fistula, intestinal obstruction and in pellagra and other nutritional deficiency states when there is an associated diarrhea

circulating blood in patients with cirrhosis of the liver is significantly lowered Pohle and Stewart (*114*) reported that in seven patients with this condition the prothrombin concentration varied between 37 and 56 per cent of normal As would be expected the administration of vitamin K therapy is ineffective in these cases when given either orally or parenterally In patients with advanced cirrhosis however it has not been my experience that the prothrombin deficiency has been an important factor in bleeding The excessive hemorrhage usually arises from ruptured esophageal varices and is readily explained on a mechanical basis The low prothrombin content of the peripheral blood however may be a factor in the continuation of the bleeding once it has been initiated It has been shown by Morlock and Hall (*115*) that thrombopenia may play a definite role in the hemorrhagic tendency noted in cirrhosis of the liver (see page 656)

Hypoprothrombinemia in Toxic Hepatitis —Since chloroform and carbon tetrachloride poisoning result in extensive damage to the liver which is accompanied by a pronounced drop in the prothrombin of the blood it is to be anticipated that toxic hepatitis due to any cause would account for this same condition This is known to be the case as indicated by the studies of Pohle and Stewart (*114*) and by Koller (*116*) and others The latter investigator reported four cases of toxic hepatitis in whom the blood prothrombin was extremely low and in whom there was no response to vitamin K administration Bleeding was not the cause of death in any of his patients

Plasma Prothrombin as an Index of Liver Function —The fact that the liver is essential to the formation of prothrombin suggests that the estimation of this substance in the blood might serve as a liver function test Studies bearing on this question were first published by Pohle and Stewart (*114*) More recently Andrus and Lord (98) in a review of the entire subject of the physiology of plasma prothrombin and its relation to liver function state that the use of the plasma prothrombin level alone for this purpose is open to serious objection This is because it may be depressed by dietary or other factors in the absence of liver damage

It has been found by Andrus and Lord (98) that the response of the plasma prothrombin to intramuscular injection of 2 methyl 1 4 naphthoquinone is a more accurate method of evaluating the function of the liver with regard to the formation of prothrombin By this method all possibility of defective absorption is eliminated from playing a role in the final result They have adopted the thesis that the level of the plasma prothrombin if below 80 per cent of normal in a given case is an index of the performance of the liver while the response of 2 mg of 2 methyl 1 4 naphthoquinone administered intramuscularly indicates whether any of this depression is or is not due to organic liver disease They found in experimentally induced chloroform poisoning in dogs that the plasma prothrombin is a far more sensitive index of liver damage than is the

Although conceivably sufficient liver damage may occur in many different conditions to cause an important degree of hypoprothrombinemia in clinical medicine the ones of greatest significance are the damage associated with obstructive jaundice with atrophic cirrhosis, and in toxic hepatitis due to various causes

After a review of the literature Lucia and Aggeler (*113*) in 1941 state that some patients afflicted with liver disease do not have hypoprothrombinemia Others with a low concentration of prothrombin in association with liver disease have an elevation of it following the administration of vitamin K whereas some are completely refractory to such treatment They were unable to demonstrate a correlation between the level of the prothrombin in the blood and the degree of liver impairment as indicated by the hippuric acid liver function test For example, some of their patients with impaired liver function as indicated by the hippuric acid test had a normal prothrombin of the circulating blood If the prothrombin was low in such cases it was sometimes elevated to normal by vitamin K therapy Regardless of these findings however, they state that in acute diseases of the liver such as acute hepatitis and acute yellow atrophy the fluctuations in the prothrombin content of the circulating blood are in proportion to the severity of the illness and are not ordinarily influenced by the administration of vitamin K Furthermore in chronic diffuse diseases of the liver such as portal cirrhosis there may be a low prothrombin concentration which is ordinarily not elevated by vitamin K therapy

Injury to the Liver in Prolonged Obstructive Jaundice —It has been demonstrated (*113*) that in a certain number of patients with obstructive jaundice, the response to vitamin K therapy has not been satisfactory The explanation of this is that in prolonged obstructive jaundice the function of the liver may be diminished to such a degree that it is unable to function normally to form prothrombin even in the presence of vitamin K The exact cause of liver damage under these circumstances is not apparent but it is assumed that the mechanical damming back of the bile is an important factor It is true that once the liver has been damaged it is more susceptible to the effects of toxic products such as produced by infection

Patients with obstructive jaundice with a hypoprothrombinemia who do not respond to the usual dose on menadione with ox or pig bile by mouth should be treated by giving synkamin in a dose of 2 to 5 milligrams daily intravenously Vitamin K_1 (Mephyton) in 50 milligram doses intravenously is probably the most efficient preparation available at present Furthermore 10 per cent glucose should be given intravenously in the hope that liver function in general may be improved If there is a complete failure by these methods then some elevation of the prothrombin level may be obtained by giving one or more blood transfusions

Hypoprothrombinemia in Atrophic Cirrhosis of the Liver —It has been found by a number of investigators that the prothrombin content of the

hemoglobin per 100 cc and 1 460 000 red blood cells per cubic millimeter Sixty three per cent of 49 clotting time determinations were prolonged sometimes as long as 55 minutes About 40 per cent of 13 determinations of clot retractions were abnormal The bleeding time was prolonged in 43 per cent of the many tests usually it was mildly prolonged but on one occasion it was more than 27 minutes The tourniquet tests were usually negative there being only two of 13 tests positive The prothrombin times were always elevated the range being from 47 to 81 seconds unless blood or plasma transfusions had recently been given

A study of the patient s family history showed that only the mother had easy bruising All members of the immediate family including the father mother sister and two brothers (another brother was not available) showed that all but the father had a prolongation of the prothrombin time This increase over the normal controls however was slight varying from 1 5 seconds to 3 5 seconds The addition of plasma to the blood of three members of the family resulted in a shortening of the prothrombin time as it did in the patient Hence it was asumed that they had a similar coagulation defect but in a different degree Special studies on the patient showed a result unlike that of hemophilia in the clotting time of recalcified plasma There was normal behavior toward the addition of purified prothrombin indicating that there was no interference with prothrombin conversion The fibrinogen content of the circulating blood was normal and the addition of dilute solutions of thrombin to decalcified plasma indicated that there was no defect in fibrinogen or an anticoagulant present The latter possibility was also eliminated by the addition of the patient s plasma to normal plasma and was *not* found to prolong the normal prothrombin time The application of the two stage prothrombin time estimation as advocated by Warner Brinkhaus and Smith indicated that the patient s deficiency was due to a lack of prothrombin and *not* due to a delayed rate of convertibility A study to determine if the deficiency was due to a lack of Component A (labile factor) which is diminished by storage or to Component B (which is removed by decumarolization in vivo and by aluminum hydroxide) Since old plasma was more effective than dicumarolized plasma in reducing the patient s prothrombin time it appears" that the more important deficiency was due to Component B (conventional prothrombin as termed by Quick) *The administration of massive doses of vitamin K oxide and menadione bisulfite demonstrated conclusively that the patient was resistant to vitamin K The injection of normal plasma or blood transfusions however produced at all time a prompt* decrease in prothrombin time It is of interest to note that blood which had been stored as long as 30 days was about as effective as blood only three days old This is additional evidence that the patient s deficiency was not of the labile factor but was of the Component B type The only

bromsulfalein test and that the latter is more sensitive than the galactose tolerance test

Idiopathic Hypoprothrombinemia —Since the first report of so-called idiopathic hypoprothrombinemia by Rhoades and Fitz Hugh (*117*), and the discovery of the Component A factor (labile factor) of prothrombin by Quick (*7*), and Factor V by Owren (*24*) it has become increasingly clear that conditions characterized by a prolongation of the prothrombin time may be due to at least two distinct clinical entities namely a deficiency of the labile factor (Factor V plasma prothrombin conversion factor) and a deficiency of prothrombin The deficiency of the PPCF (labile factor) can be of the congenital or acquired type as is described elsewhere (see page 537) The congenital type is a rare condition and has been described by Rhoades and Fitz Hugh (*117*), and Hagen and Watson (*118*) as idiopathic (familial) hypothrombinemia and by Owren as parahemophilia (*119*) Acquired depletion of the labile factor is found in liver dysfunction acute and chronic leukemia pernicious anemia and in some instances in dicumarol deficiency in man (*120*)

The case reported by Rhoades and Fitz Hugh (*117*) was in a boy who had been observed from the age of six years until his death at the age of 16 years A diagnosis of hemophilia had been made on the basis of a prolonged coagulation time which on one occasion was as great as 75 minutes Abnormal bleeding had occurred at various sites including the elbows the lips into the kidney (hematuria) Finally death resulted from a subdural hematoma and hemorrhage into the left basal ganglion Although the patient had been regarded as having hemophilia for the past 10 years there was no family history of the disorder and in 1938 when Quick s method of performing the prothrombin time was introduced it was found that it varied between 70 to 90 seconds Vitamin K therapy was given orally and parenterally without raising the prothrombin content of the circulating blood Several liver function tests were found to be normal The case differed from the typical one of hemophilia in that clot retraction was poor At necropsy there was nothing found to account for the abnormal bleeding

A comprehensive study of a patient with idiopathic hypoprothrombinemia has been made by Hagen and Watson (*118*) and the data pertaining to previous cases summarized Their patient was a female domestic of Swedish descent who had the onset of her disease at the age of two years with a swollen discolored painful left knee She was 20 years old when first observed From that time until the last period of observation (a total interval of 29 years) the patient had prominent manifestations of a hemorrhagic tendency characterized by epistaxes subcutaneous hemorrhages bleeding in the proximity of various joints and menorrhagia and metorrhagia the latter being so severe as to require hysterectomy Following profuse uterine bleeding the blood values fell as low as 4 4 grams of

recent authoritative summary dealing with this subject is the one by Wright (129) He cites the results of a study involving 2915 patients with coronary thrombosis and myocardial infarction of whom 1242 were treated with dicumarol and 1673 served as untreated controls An inspection of the results are convincing for there was a mortality of 15 3 per cent with thrombo embolism in 8 1 per cent in the untreated group as compared with a mortality of 25 7 per cent and thrombo embolism in 22 1 per cent in the controls Furthermore Wright is convinced that anticoagulant therapy is the treatment of choice in the great majority of patients with thrombophlebitis with or without embolic episodes that patients with rheumatic heart disease who have auricular fibrillation and multiple embolization should be kept on ambulatory anticoagulant therapy to prevent continued propagation of the mural thrombi and continued embolization and that there is accumulating evidence to indicate that the use of anticoagulants in patients with congestive heart failure is sound Wright warns (129) that there will be some failures with each anticoagulant that a uniform response to a given dose cannot be obtained in all patients and finally that the use of any anticoagulant is attended with a certain risk of hemorrhage He emphasizes that there are no contraindications to the administration of anticoagulants provided the physician knows how to employ the preparations and if use is made of accurate facilities for the determination of the prothrombin concentrations and coagulation time

Anticoagulant Treatment of Myocardial Infarction —As dicumarol has a latent period of 12 to 24 hours before the prothrombin concentration of the circulating blood is decreased it is my opinion that a more rapidly acting anticoagulant heparin should be administered as soon as the diagnosis is established in all patients with coronary thrombosis and associated myocardial infarction The usual plan which has been followed at the University of Michigan Hospital under the direction of Dr Ivan Duff is as follows a patient with this condition is given 50 to 75 milligrams of heparin intravenously and at the same time "depot heparin is injected intramuscularly The intravenous heparin prolongs the clotting time within 10 to 15 minutes and its action persists for about three to four hours An intramuscular dose of depot heparin of 400 milligrams is given if the patient s body weight is over 140 pounds or 200 milligrams if it is less than 140 pounds This is repeated approximately every six to eight hours until the 300 milligram dose of dicumarol which is given orally as soon as the patient is seen has time to act Due to the latent period of at least 12 to 24 hours before dicumarol begins to act and as the maximum effect may not be attained for as long as 72 hours it is usually safe to give a dose of 300 milligrams of dicumarol as soon as the patient is seen and to give 200 milligrams the following day Subsequent dosage is then guided by the concentration of prothrombin *Under no circumstances should the drug be administered in the acute*

possible etiologic factors which are suggested by extensive studies of this patient were positive cephalin flocculation tests and the presence of a cyroglobulin in the blood plasma. These findings pointed to the possibility that a primary disturbance of protein synthesis in the liver may have been present.

The treatment of idiopathic hypoprothrombinemia is unsatisfactory as it is apparently refractory to vitamin K therapy in large doses regardless of the route of administration. The only form of therapy which is even of transient benefit is the repeated tranfusion of blood or plasma.

The Effect of Dicoumarin and Heparin on the Clotting Process Toxic Sweet Clover Disease in Cattle.—Although it had been known for many years by veterinarians and stock raisers that cattle were subject to a disease characterized by excessive and sometimes fatal bleeding, it was not until 1922 that Schofield (*121, 122*) of the Ontario Veterinary College made a scientific study of the condition. He reported that the disorder developed following the feeding of improperly prepared hay or silage made from the common sweet clovers. It was also determined that the condition could be alleviated, if it had not proceeded too far, by the *withdrawal of the spoiled hay from the diet or in some instances, by the* injection of freshly drawn normal blood serum from healthy animals. Schofield attributed the condition to molds but *did mention that fact that sweet clover was known to contain coumarin*. Furthermore, this investigator demonstrated that the blood showed delayed clotting which he thought was due to lack of thrombin or some inhibitory agent. Roderick (*123, 124, 125*) discovered that the abnormal tendency to bleed was associated with a decrease in the amount of the circulating prothrombin of the blood and he too advocated the injection of normal fresh cattle serum in the control of the condition. This was confirmed by Quick (65) who found that a pronounced drop occurred in the prothrombin content of the blood within two days after feeding the spoiled hay and that hemorrhages occurred when the prothrombin fell to a low level. Following this work the group of investigators (*126, 127*) at the Wisconsin Experimental Station isolated and synthesized the hemorrhagic agent 3,3 *methylene bis (4 hydroxycoumarin)*.

Effects of Dicoumarin Administration in Man.—The interest in this hemorrhagic agent is its effects on the prothrombin and clotting processes of the blood and its possible therapeutic uses as an anticoagulant in the treatment and prevention of thrombosis, embolism and various vascular disorders in humans. The possibility of dicumarol as a means of providing anticoagulant therapy was recognized soon after 1940 when the drug was first isolated in crystalline form. In 1941 the initial clinical trial was reported by Butt, Allen and Bollman (*128*). Since then in the interval of 11 years the drug has been used in many patients and an opportunity afforded to evaluate its effectiveness. A most comprehensive

was deficient at the end of two hours The prothrombin time (Quick one stage method) was prolonged to 500 seconds on one determination and 800 on another whereas the control had a normal time of 16 seconds There was such a great depletion of prothrombin that it was not possible to express the percentage of concentration from the standard dilution curve The patient was given 1000 cc of blood and 72 milligrams of vitamin K (Hykinone) intravenously every three hours a total of 222 milligrams being injected within 14 hours The prothrombin time at necropsy four hours after death was 85 seconds as compared with a normal control of 16 seconds The prothrombin concentration was estimated to be less than 5 per cent of normal Necropsy disclosed cerebral subarachnoid cardiac renal hepatic pulmonary periosteal retroperitoneal and cutaneous hemorrhages The authors concluded that the most important contraindication to the use of dicumarol is the lack of proper laboratory facilities They also emphasize that caution should be observed in the administration of dicumarol to patients with severe hypertension especially if there is a past history of cerebral vascular accidents

Two cases with toxic effects attributed to dicumarol have been reported by Powers (*131*) One patient with congestive failure and gangrene of the feet had extensive rectal hemorrhages following dicumarol therapy although the prothrombin concentration did not fall below 12 per cent The patient made a prompt recovery from the tendency to bleed following the discontinuance of the dicumarol and the administration of menadione The second patient who had rheumatic heart disease was given dicumarol therapy on the basis of a diagnosis of infarct of the lung The drug was administered in standard dosage over a period of 27 days at which time there developed a persistent epistaxis associated with a prothrombin time as low as 7 per cent Despite large doses of Hykinone (menadione sodium bisulfite) the patient succumbed Necropsy showed in addition to rheumatic valvular disease hemorrhages in the pelvis the peritoneum the parietal pericardium and in the lungs and bronchi This observer concludes that in these two patients chronic passive congestion interfered with the synthesis of prothrombin in the liver to such an extent that conservative doses of dicumarol produced excessive bleeding In addition it was his opinion that diminished renal filtration due to congestive failure caused a retention of dicumarol which was responsible at least in the past for the toxic effects

Newer Anticoagulants—In recent years a number of newer anticoagulants have been introduced in the hope that one or more of the defects of dicumarol might be corrected The chief difficulties with dicumarol are 1 too much time is required for the drug to act 2 and after it is discontinued the anticoagulant effect persists too long

cases unless it is possible to be guided by accurate prothrombin determinations done daily by an experienced technician The objective should be to keep the prothrombin concentration as determined by the Quick one stage method below 30 per cent at which level thrombosis usually does not occur and above 10 per cent at which level hemorrhage is rarely observed Usually the anticoagulant therapy is continued for a period of about three weeks The ambulatory treatment of certain conditions *such as venous thrombosis* or a *rheumatic heart disease* with auricular fibrillation and thrombo embolic phenomena with anticoagulant therapy should be carried out with extreme caution This should be attempted only with cooperative patients who have been on a stabilized dosage and in those who will report for frequent determinations of the prothrombin in the circulating blood

Contraindications to the Use of Dicumarol —The only danger in the use of dicumarol is the hazard of excessive hemorrhage The LD_{50} of dicumarol for various animals when the drug is given intravenously is about 50 milligrams per kilo of body weight Death occurs within a few hours prior to any change in the prothrombin concentration Orally the LD_{50} is much greater and a fatal result does not occur for several days (*130*) Care should be used however in administering the drug to patients with an obvious hemorrhagic tendency or with open wounds or ulcerations especially of the gastro intestinal tract Furthermore such therapy should not be used in patients who have had recent brain operations or a cerebral hemorrhage Dicumarol should be given with caution in patients who have extensive liver disease as the synthesis of prothrombin may already be impaired It is known also that the presence of renal disease unduly prolongs the action of the drug and hence untoward effects in such patients may result from a standard dosage The possibility that hemorrhage *in utero* in pregnant women may result from dicumarol therapy should be kept in mind None of these conditions named are absolute contraindications however but their presence makes it necessary that the situation be carefully considered to estimate the possibility of harm as compared with the likelihood of benefit

There is no question but what the careless use of the drug may cause serious bleeding and death in some instances For example Duff and Shull (*73*) report a fatal case and review the findings in 21 cases in the literature and in one additional case which had not previously been reported In their patient a 36 year old woman dicumarol had been administered on account of pain and swelling in both legs It was estimated that 300 milligrams had been given by mouth daily for a period of approximately 37 days making a total dosage of 11 1 grams in that period The patient developed blood streaked sputum bleeding from the mouth and vagina and finally a gross hematuria The hemoglobin was 9 0 grams the bleeding time (Ivy method) seven minutes the clotting time (Lee White) was prolonged to 48 minutes and the clot retraction

a nephrectomy or suffered renal damage are abnormally sensitive to the drug

It is known that dicumarol impairs the clotting mechanism by reducing the prothrombin content of the circulating blood The exact method by which this is accomplished however is uncertain One theory suggested by Woolley (*143*) is that dicumarol and vitamin K have somewhat similar structures the former might act by competing with the latter in the reactions concerned with the formation of prothrombin This theory is based largely on inference and lacks substantial proof Another theory is that the drug has a toxic effect on the liver (*144A*) but proof in support of this is not available It is certain that dicumarol does produce a hypoprothrombinemia and the mode of action is on the liver but no additional positive statement can be made in regard to its mode of action at present An excellent review of our knowledge concerning dicumarol is given by Riggs (*142*) and by Smith (*145*)

Heparin —This substance a highly effective anticoagulant in vitro and in vivo was discovered in 1916 by McLean (*146*) a second year medical student working in the physiology laboratory of William H Howell the Professor of Physiology of Johns Hopkins University Extensive studies of the material were made in subsequent years by Howell (*147 148 149 150*) As it had a comparatively high concentration in the liver he gave it the name of heparin

Although much has been learned in the intervening years there is still uncertainty concerning its exact chemical structure and its mode of action in preventing coagulating An extensive summary of our knowledge concerning heparin has been written by Jorpes (*144*) and shorter articles of a similar nature have been published by Riggs (*151*) and by Smith (*145*)

The fact that heparin is a carbohydrate was established by Howell who also described methods for its extraction and purification (*150*) Although heparin was originally prepared from liver it has now been possible to utilize beef lung in a process which yields a purified product more readily and at a much lower cost In 1940 Charles and Todd (*152*) concluded that it was a mucoitin sulfuric acid in which the basic tetrasaccharide unit contains five sulfuric ester groupings It is the opinion of Jorpes (*144*) that the substance is mucoitin tri sulfuric acid but he is inclined to doubt that any heparin sample thus far produced consists of a single molecular species The compound is strongly acidic and electronegative It has the property of forming stable salts with proteins This characteristic possibly accounts for its action of altering the enzymes concerned with coagulation of the blood It is likely that this property also explains why it is bound and inactivated by highly basic proteins such as protamines Toluidine blue a basic dye also has the ability to combine with heparin thereby forming a poorly disassoci

3 the effect of any given dose is somewhat uncertain It is possible that one or more of the following drugs will prove to be of greater value than dicumarol as preliminary trials indicate that a number of them have promise It is too soon however, to draw any definite conclusions at present Furthermore, it is likely that synthetic chemistry will develop even more effective anticoagulant drugs in the not too distant future

Of the new anticoagulants which have been introduced since dicumarol was first used is *Tromexan* (3 3 Carboxymethylenebis (4 hydroxy coumarin) (*132, 133, 134*) *Phenylindanedione* (Danilone P I D) was *first studied in animals by Kabat Stohlman, and Smith (135) more* recently Blaustein *et al* (*136*) have reported their clinical experience with the drug *4 Hydroxycoumarin Anticoagulant No 63* was synthesized in Link s laboratory by Ikawa in 1942 (*137*), and observations on the effect of this anticoagulant have been reported by Battle and his associates (*138*) *Paritol* which is a synthetic polysulfuric acid ester of poly anhydromannuronic acid, resembles heparin in both chemical structure and *in its action Studies on this drug have been reported by Marple* and Wright (*139*) While all of these preparations undoubtedly have some merit it is not possible at this time to evaluate them definitely Our own studies at the University of Michigan Hospital supervised by Dr Ivan Duff are chiefly with Phenylindanedione (P I D) Preliminary observations suggest that it can produce an anticoagulant effect sooner than dicumarol and that the results are more predictable Further observations are necessary however before any final statement can be made concerning its efficacy

An excellent discussion of the newer anticoagulants is given by a number of authorities in this field in the *Transactions of the Third Conference* January 23–24 1950 sponsored by the Josiah Macy Jr Foundation dealing with Blood Clotting and Allied Problems

Chemical Characteristics and Mode of Action of Dicumarol —Dicumarol is a whitish or slightly buff colored crystalline solid which is almost completely insoluble in water but forms soluble salts with alkalis Chemically it is 3 3 methyl bis (4 hydroxycoumarin) Coumarin is a compound widely distributed in the vegetable kingdom On fusion with potassium *each molecule of dicumarol yields two molecules of salicylic* acid It is almost insoluble in water and hence is not suited for parenteral injection When given orally it is absorbed but at a slow rate Apparently it is utilized in the body to some extent when given rectally (*140*)

In the plasma it is completely bound to protein and also is combined to a high degree in the tissues *It is metabolized slowly* and only traces appear as such in the urine According to Overman *et al* (*141*) no *dicumarol could be demonstrated* in the urine of dogs when they had been given 400 milligrams a day for six days It should be kept in mind as emphasized by Riggs (*142*) that despite this *patients who have had*

to three hours. A small portion of the material is excreted in the urine (159) but probably most of it is destroyed by an enzyme (heparinase) which is found in body tissues (*160*).

As it is known that comparatively large quantities of heparin are stored in the tissues of the body, especially the lungs and the liver, it is suggested that it has a physiological function. As yet, however, this has not been proven.

Heparin for clinical use is available as the sodium salt in sterile 10 cc ampules containing 10 milligrams per cc and with a potency of not less than 100 units per milligram of the dry material. It is given intravenously as a rule but in recent years preparations for subcutaneous and intramuscular use have been employed (*161, 162*). Prolongation of the effect over that obtained by the intravenous injection may be attained by the use of "depot" or repository preparations as suggested by Loewe *et al.* (*163, 164*). One difficulty in the use of such substances, however, is the unpredictability of the action. For example, it is reported by Vorzimer, Sussman and Marder (*162*) that in a group of eight patients who were given a single dose, 300 milligrams of heparin emulsified in a mixture of cholesterol derivatives, peanut oil and beeswax, the maximum clotting time varied from 400 to 1400 per cent of the control value and the duration of the action persisted from 15 to 24 hours.

The only real danger of heparin administration is from excessive hemorrhage which large doses may cause. It does cause considerable pain and tenderness which persist for 24 to 36 hours when given intramuscularly as "depot" heparin. As much as 500 milligrams in a single dose have been injected into a rabbit intravenously without untoward effects. Although it readily combines with protein, no antigenic effect has been noted in animals (*128*) and anaphylactic reactions are exceedingly rare in humans.

Hemorrhagic Diathesis Due to Circulating Anticoagulants.—The first patient observed to have an abnormal bleeding tendency due to a circulating anticoagulant was reported by Lozner, Jolliffe and Taylor in 1940 (*165*) although such a possibility has been previously suggested in 1925 (*166*) and in 1927 (*167*). Eleven cases have been reported according to Pons and DeTorregrosa (*168*) since that time and they have observed the twelfth. These authors summarize the literature and emphasize that the disease may occur more frequently than had previously been supposed. They state that the cases have been in adults between the ages of 21 to 66 years and all but three were males. The clinical course is characterized by multiple spontaneous hemorrhagic phenomena. The blood showed only three changes of importance, namely, 1, marked prolongation of the venous clotting time, 2, an anemia following some of the hemorrhages and 3, the ability of minute amounts of the blood or plasma of these patients to prolong the coagula-

ated insoluble salt of heparin, and, like protamine, almost instantly reversing the anticoagulant action of heparin

There is strongly suggestive evidence that heparin is produced in the body by granules of Ehrlich's mast cells which are known to be distributed close to the capillaries in various tissues of the body. The heparin content in various parts of the body shows a definite correlation depending on the number of mast cells in the different tissues according to Jorpes, Holmgren and Wilander (*153*). Furthermore they have found that when the state of anaphylactic shock is produced there is liberation of heparin into the circulating blood with a disappearance of the metachromatic granules from the hepatic mast cells.

The anticoagulant action of heparin is not clearly understood. This substance has indeed a most remarkable ability to prevent blood from clotting. For example it is estimated (*154*) that its action is more efficient than any other known anticoagulant substance as one part of heparin will prevent the clotting of 100 000 times its weight in blood. It is known that in heparinized blood the conversion of prothrombin to thrombin does not occur but if thromboplastin is added coagulation immediately is accomplished. In other words heparin acts to prevent the formation of thrombin from prothrombin. This action was originally explained by Howell (*155*) on the basis that heparin combines with prothrombin to form a complex from which heparin can be removed by an excess of thromboplastin. As pointed out by Riggs (*151*) it is equally possible however that heparin prevents the formation of thrombin by combining directly with thromboplastin and thereby preventing it from activating prothrombin. It seems to be clear as Ferguson has emphasized (*156*) that the antagonism between heparin and thromboplastin is quantitative and mutual, an excess of either nullifies the action of the other.

Heparin also has another action in that it acts as an antithrombic agent in the presence of the normal co factor of serum. It should be kept in mind that heparin alone has little if any effect on the isolated components of the clotting system but requires the presence of a co-factor which is present in the crude albumin fraction of plasma although it is not present in pure crystalline albumin (*157*). It is thought to be a euglobulin by Loomis (*158*). The anticoagulant action of heparin can be reversed almost instantly by toluidine blue or protamine which are basic substances that form insoluble salts of heparin. These have been employed to combat hemorrhage due to excessive amounts of heparin in the blood stream.

Heparin is ineffective orally and must be given parenterally. When injected intravenously in a single dose sufficient to prolong the coagulation time to 30 minutes there is a latent period of about 10 minutes before the anticoagulant effect is apparent, the action disappears in two

of protamine be administered to neutralize a dose of 200 milligrams of heparin given in the preceding one to three hours. This amount of protamine will probably be effective as heparin is rapidly destroyed in the body. It is suggested that the protamine be injected in 50 cc of saline intravenously over an interval of five to fifteen minutes. If the patient has received large doses of heparin it may be necessary to repeat the dose within one hour. They emphasize that the action of intravenous heparin is usually brief and hence seldom requires protamine neutralization but overdosage of intramuscular heparin especially when in a menstruum is a greater hazard on account of the possibility of producing a prolonged elevation of the coagulation time to dangerous levels.

It is the recommendation of Enerson and Allen (*170*) that protamine sulfate be given in uncomplicated bleeding states, with associated abnormal protamine titration findings such as in postpartum bleeding and menorrhagia. In the former 50 milligrams may be given every four hours intramuscularly until the bleeding is controlled. Fifty milligrams may be injected intramuscularly every four hours for one or two injections on the second day of the period in patients with menorrhagia. In some instances there is a response to oral therapy. Toluidine blue is usually more effective in bleeding conditions associated with a depression of the bone marrow elements such as may be observed in thrombocytopenic purpura and leukemia. It is recommended that 8 to 10 cc per kilogram of a 0.04 per cent solution in saline be given intravenously twice daily in such conditions. They admit however for reasons which are not understood that there may be a poor response to either toluidine blue or protamine injection even when protamine titration is abnormal.

It is of interest that in *anaphylactic shock* the blood does not coagulate normally and this has been attributed to the release of heparin into the circulating blood. This receives substantial support by the isolation of crystalline heparin from the blood of dogs in which such a condition has been induced experimentally (*175*) and by the observation that this substance cannot be isolated from the blood of normal dogs.

In the *postirradiation syndrome* produced experimentally in dogs it is reported by Allen, Moulder and Enerson (*176*) that the hemorrhage thus induced is in some instances associated with a circulating anticoagulant but in others no evidence of such an inhibitor can be found although coagulation may be greatly delayed. It is also concluded by these observers that in some respects but not all the physiological action of the circulating anticoagulant resembles heparin of the commercial type. They concluded that possibly other nonheparinoid substances are also present but thus far none have been identified. In some animals the hemorrhage responds partially and less often completely to the administration of toluidine blue and to a smaller extent to protamine sulfate. It is recommended therefore that the therapeutic use

tion time of normal blood which was taken as an indication of a circulating anticoagulant. Although in some of the patients there was considerable disability due to frequent and severe hemorrhages the condition may persist for long periods of time. Two of the patients were reported to have survived for periods of nine and 20 years respectively although no therapeutic measures have been discovered which affect the course of the disease favorably.

A 40 year old woman was reported by Pons and DeTorregrosa *(168)* who had a hemorrhagic diathesis which they attributed to the presence of an anticoagulant in the circulating blood. This substance was shown to be active in dilution up to 1 350 and its potency was retained after heating to 61 degrees C for 10 minutes and after storage either in a refrigerator or at room temperature for 24 hours. Neither protamine sulfate nor toluidine blue neutralized the anticoagulant. Placental plasma corrected the clotting defect in vitro but had no effect when given to the patient intravenously. In their opinion the second and third stages of clotting were normal in this patient but they belive that the patient's plasma had antithromboplastic activity and that the anticoagulant might be antithromboplastin.

Recently interest has been aroused in the so called *heparinoid* states in which a heparin like substance has been demonstrated in the circulating blood of patients as the only demonstrable cause of the abnormal bleeding. The studies of Allen made with the protamine titration test of Allen and his associates *(169)* permit a quantitative estimation of the circulating heparinoid material and according to this investigator indicate that such a substance or substances is a contributing factor in many clinical conditions associated with abnormal bleeding. Such a change has been reported in thrombocytopenic purpura *(170)* post partum hemorrhage *(171)* in menorrhagia *(172)* and in leukemia lymphosarcoma aplastic anemia Hodgkin's disease and other blood disorders *(173 174)*.

According to Enerson and Allen *(170)* the exact nature of the substance measured by the protamine titration test is not known but they believe it is an anticoagulant resembling but not identical with heparin. They state that most of these cases showed a response to the injection of protamine sulfate or the basic aniline dye toluidine blue with a change in the protamine titration or improvement in the clinical condition of the patient.

Overheparinization may result when commercial heparin is administered in the treatment of patients with coronary thrombosis or other thrombotic conditions. Such a state can be remedied almost immediately by the intravenous administration of protamine sulfate. As protamine combines with and inactivates heparin on approximately a 1 1 basis it is recommended by Enerson and Allen *(170)* that 50 to 100 milligrams

of protamine be administered to neutralize a dose of 200 milligrams of heparin given in the preceding one to three hours This amount of protamine will probably be effective as heparin is rapidly destroyed in the body It is suggested that the protamine be injected in 50 cc of saline intravenously over an interval of five to fifteen minutes If the patient has received large doses of heparin it may be necessary to repeat the dose within one hour They emphasize that the action of intravenous heparin is usually brief and hence seldom requires protamine neutralization but overdosage of intramuscular heparin especially when in a menstruum is a greater hazard on account of the possibility of producing a prolonged elevation of the coagulation time to dangerous levels

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of these materials be considered in conditions in which there is a heparinoid defect although the therapeutic effect is unpredictable In man they recommend the use of toluidine blue intravenously in daily *doses of 5 to 7 milligrams per kilo of body weight during the bleeding* period Protamine, although more rapid in action is less effective The duration of its action is less than two hours whereas that of toluidine *blue is 24 to 26 hours*

Treatment of Excessive Doses of Anticoagulants—When a large amount of dicumarol has been given and the prothrombin concentration *falls below 10 per cent of normal the possibility of spontaneous hemor*rhage must be considered If the patient has an ulcerative process in some part of the body as for example the gastro intestinal tract the *likelihood of hemorrhage is greater* The treatment of such a condition consists of the use of blood or plasma giving 1000 cc if the condition of the patient is serious and the administration of menadione sodium bi*sulfite U S P (Hykinone) 72 milligrams intravenously every four hours* for six to eight doses It is claimed by James and his associates *(177)* that vitamin K_1 oxide is superior to Hykinone and Synkavvite in reversing *dicumarol hypoprothrombinemia and their published data give strong* support to this statement Recently the value of a 5 per cent emulsion of vitamin K_1 given intravenously to patients with a dicumarol induced *hypoprothrombinemia has been demonstrated by Watkin and his associates (178)*

Vitamin K_1 *is superior to menadione and related compounds (179 180)* *in reversing the anticoagulant action of dicumarol like drugs* and phenyl indandione A preparation of vitamin K_1 in the form of an aqueous emul*sion of vitamin K_1 is now marketed commercially by* Merck and Company *under the trade name of Mephyton* This product is available in 1 0 cc ampules each cc containing 50 milligrams of vitamin K_1 It is claimed that this preparation has an effect within a few minutes when a prothrombin deficiency *is due to dicumerol or related compounds* and that bleeding is usually terminated within three hours The drug may be given in doses of 100 to 150 milligrams by slow intravenous grip in patients with hemorrhage or in doses of 50 milligrams if the prothrombin level has been reduced to a dangerous level but bleeding is not present It is recommended that the material be injected intravenously at a rate which does not exceed 10 milligrams per minute and to facilitate the slow administration it may be mixed with sterile water or isotonic saline solution

Hemorrhage associated with an excessive *dosage of heparin* may be corrected immediately by the administration of protamine *sulfate* It is known that protamine combines and inactivates heparin on approximately a 1 1 basis *(170)* Hence at the time of overdosage the amount of protamine required *is equal in weight to the heparin excess* As

heparin is destroyed rapidly in the body a dose of 50 to 100 milligrams of protamine is sufficient to neutralize an overdosage of as much as 200 milligrams of heparin given in the preceding one to three hours. The protamine is given in about 50 cc of saline intravenously over an interval of five to 15 minutes. If large doses of heparin have been administered it may be necessary to repeat the dose of protamine in one hour. Intravenous heparin is transient in its effect and rarely requires neutralization but when the material is given intramuscularly the hazard is greater because there is a prolonged elevation of the clotting time to levels which are dangerous.

Thromboplastin.—The origin and nature of thromboplastin has been the subject of considerable investigation and speculation. It has a wide distribution in the body as an intracellular substance which can be demonstrated whenever tissue cells are ruptured or injured. Its greatest concentration in the body is in the brain, lungs, testes and thymus.

It is not present in the blood in any considerable quantity in vivo obviously if it were present in the active form intravascular clotting would occur. Thromboplastin contains or is in close association with a lipoid and has as its main function a participation in the conversion of prothrombin to thrombin. According to MacFarlane (*181*) the rate of thrombin generation is determined largely by the concentration of thromboplastin and the total quantity which is ultimately formed is proportional to the amount of prothrombin which is present.

The relation of thromboplastin to clotting by the use of silicone coated needles and syringes is discussed by Jaques (*182*). Blood thus obtained when transferred to silicone coated tubes has a clotting time of 30 to 70 minutes at 37 degrees C. The clotting time when the blood is transferred to ordinary glass tubes is about 10 minutes. The addition of thromboplastin obtained from rabbit brain reduces the clotting time to 20 seconds. It is thought (*182*) that the long clotting time in silicon tubes is due to the absence of thromboplastin at the time the blood is drawn. When normal blood without the addition of tissue thromboplastin comes in contact with glass there is a disintegration of platelets which liberates thromboplastin and consequently reduces the clotting time to 10 minutes. Or as Jaques says (*182*) platelets as a source of thromboplastin can reduce the clotting time to 10 minutes whereas damaged tissue can reduce it to 20 seconds.

The relation of the blood platelets to the clotting of blood is not entirely known at present. For example some investigators (*183 184*) have maintained that all of the components necessary for clotting are present in platelet free plasma and that the coagulation process can be initiated in the absence of platelets. It has been shown by Conley and his associates that plasma free from platelets clots in a short time when brought in contact with glass tubes which have a relatively rough surface

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The possibility that the man described by Henry Banyer (*190*) presented before the Royal Society of London on December 22 1743 had hemophilia is great. He gives the details of the case of "a gardner about the age of 24 years who bled excessively from a minor injury to the foot from the bowels from the urinary tract and from the nose The patient finally succumbed nine years after his first reported hemorrhage from a lethal loss of blood due to a slight wound somewhere on one of his legs" It is regrettable that no mention is made of this patient's condition prior to the age of 24 years when the first abnormal tendency to bleed was noticed

In 1803 Dr John C Otto (*191*) of Philadelphia contributed in three and one half brief pages a medical classic which is regarded by some as the initial description of hemophilia containing many of the important essential characteristics of the disease He collected information in regard to the descendants in New Hampshire of "a woman by the name of Smith who transmitted the following idiosyncrasy to her descendants If the slightest scratch is made on the skin of some of them as mortal a hemorrhage will eventually ensue as if the largest wound is inflicted He also made the following points in regard to the nature of the disease for the first time namely that "the males only are subject to this strange affection" and all of them are not liable to it Although the females are exempt they are still capable of transmitting it to their male children Otto was probably the first to use the name in medical literature "bleeder" as applied to these patients It is of interest to note that although Otto gave all of this information accurately there is no evidence to indicate that he examined or even saw any of the affected persons

In 1820 Nasse (*192*) published his paper in which most of the recorded cases of the disease were collected and the general law bearing his name which deals with the transmission of the disease was formulated

According to Legg (*187*) Schonlein's influence at this time began to be felt The name hemophilia was proposed by Schonlein in 1839 and under his teaching a number of inaugural dissertations on hemophilia were published at Wurzberg and Berlin The monograph of Ludwig Grandidier *Die Hemophilie* containing his valuable statistics appeared in 1855 The treatise on hemophilia by Wickham Legg was published in London in 1872 and gives an accurate resume of our knowledge of the disease up to that time

In 1893 A E Wright (*193*) then Professor of Pathology at the Army Medical School Netley England determined by means of an original capillary tube method that the clotting time was prolonged to over one hour" in a patient with the disease whereas the normal clotting time by this method was two and one half to six minutes

whereas clotting of the same plasma in silicone treated tubes is greatly prolonged and sometimes there is no clotting at all Their observations suggest in their opinion, that contact with glass activates some plasma constituent which can initiate the coagulation process Although they are unable to give any information concerning the origin or nature of this plasma factor they believe that an inactive thromboplastin pre cursor *in plasma is activated on contact with glass surfaces* These investigators call attention to the possibility that a few platelets may have broken up in the manipulations involved in their experiments and this may have played a greater role in their result than has been attributed to it The balance of evidence still indicates however, that the initial change in the clotting process in vivo arises in the disintegration of the blood platelets and that this results in the liberation of some substance *probably an enzyme which activates or in some way makes available* inactive thromboplastin

It is stated by Quick *(185)* that normal blood does not contain free or active thromboplastin Thromboplastinogen, its inactive precursor, however is present In his opinion the essential role of the platelets is the activation of thromboplastinogen by thromboplastinogenase an enzyme which they liberate

HEMOPHILIA

Definition —Hemophilia is a disease due to an hereditary anomaly of blood *which is characterized by a delayed coagulation with resultant* abnormal bleeding It appears only in males is transmitted by females and behaves as a sex linked recessive mendelian factor

History —The earliest reference to hemophilia is undoubtedly to be found in the Babylonian Talmud *(186)* in which there are several references given which are dispensations for circumcision According to Legg *(187)*, there was no notice of hemophilia by Greek or Latin authors He states that the earliest account is to be found in the records of Albucasis an Arabic author who died in Cordova in 1107 A D In his writings it is related that in a certain village there were men who suffered an uncontrollable hemorrhage if wounded or phlebotomized which terminated fatally The same accident happened to the boys of the village if their gums were harshly rubbed There is considerable doubt in my mind if this description is one of patients suffering with hemophilia Virchow *(188)* refers to the writings of Philip Hoechstetter *(189)* a physician practicing in Augsburg at the beginning of the seventeenth century who describes the case of a boy who is said to have suffered from nasal hemorrhage repeated epistaxes bloody stools and spontaneous ecchymoses *This is the best description of the older cases and probably repre* sents a true instance of hemophilia

been determined by Pickering (*200*) in confirmation of previous work by Howell (*198*) that when saponin is added to hemophilic blood causing a complete disintegration of platelets normal clotting is not restored Furthermore Quick (*201*) found that the addition of hemophilic platelets to platelet poor normal plasma caused normal clotting On the basis of these observations Quick (*202*) has concluded that the fault is not in the platelets but in the precursor of thromboplastin the inactive thromboplastinogen found in the circulating plasma According to Castle (*203*) at least by definition it (thromboplastinogen) is identical with the antihemophilic globulin of Patek Taylor and their associates"

In 1937 Patek and Taylor (*204*) determined that the antihemophilic activity of normal plasma was associated with the euglobulins of the circulating blood and this has been confirmed subsequently by a number of investigators (*205 206 207*) It is present especially in fraction I but is also present in fraction III 2 according to the Cohn nomenclature (*208*) When fraction I is injected intravenously it has been demonstrated that it has antihemophilic activity

In the opinion of Tocantins (*209 210*) the thromboplastin deficiency in hemophilia is due to the action of an anticoagulant He bases this conclusion on the finding that normal plasma has the ability to reduce the clot accelerating action of brain extracts (cephalin) and determining that this anticephalin activity in hemophilic plasma is excessive

In summary this may be said in relation to the etiology of hemophilia The essential abnormality in the blood is the prolonged clotting time This is due to a defect in the formation of thromboplastin and hence the conversion of prothrombin to thrombin is inefficient The exact abnormality responsible for the faulty production of thromboplastin is unknown It may be due to a deficiency of a plasma constituent (thromboplastinogen antihemophilic globulin) or to an excessive amount of circulating antithromboplastin (anticephalin) or to both The defect is definitely related solely to the elaboration of thromboplastin as all other clotting components are known to be normal

Canine Hemophilia —Apparently a disease identical with human hemophilia occurs in dogs This was first recognized by Field Rickard and Hutt (*211*) and has been extensively studied by Brinkhous and his associates (*212*) The condition in canines is recognized by the characteristic hemorrhagic phenomena the prolonged clotting time the chronic recurring hemarthrosis and with the occurrence limited to male offspring of certain female carriers It has been reported by Graham *et al* (*213*) that unless the bleeding tendency is controlled by transfusions with normal blood or plasma the animals die of massive hemorrhages in the first few months of life By breeding experiments it has been possible to confirm the opinion that in humans the disease is inherited as a recessive sex linked characteristic For example when transmitter

Between the years 1890 and 1894, Frantz Konig (*194*) published descriptions of joint involvement in patients with the condition

There are several monographs dealing with the disease That of Bulloch and Fildes (*195*) published in 1911, makes a careful survey of all the work done on the disorder to that time In 1930 H Schloessmann published his monumental work *Die Hamophilie* (*196*) a monograph of 306 pages with nine and one half pages of bibliography The most recent monograph on the subject is an excellent one with profuse illustrations by Carroll L Birch which was published in 1937 (*197*)

Etiology —It is now generally agreed that the cause of the delayed *coagulation time is a deficiency of thromboplastin in the circulating blood which retards the activation of prothrombin to thrombin* thereby causing a prolongation of coagulation time That the defect in the blood is due to a decreased amount of thromboplastin is indicated by the observation that the addition of thromboplastin in the form of lung extract will cause the blood from a patient with hemophilia to clot within two minutes whereas spontaneous clotting does not occur for one or more hours Furthermore this view is supported by the observation that clotting will occur normally when the patient is transfused with the plasma of normal blood It is not thought that there is a complete absence of thromboplastin in patients with the disease for eventually the blood will clot Furthermore it is possible to prepare thromboplastin from hemophilic plasma which will cause clotting but the process will be much slower than when it is prepared from normal plasma

Howell (*198*) is of the opinion that thromboplastin is supplied normally to the blood plasma by the disintegration of the circulating blood platelets Apparently there is no difference in the amount of thromboplastin contained in normal platelets and in those contained in the blood of a patient with hemophilia This can be demonstrated by treating the platelets obtained from the blood of a patient with hemophilia with a slightly alkaline saline solution which apparently liberates thromboplastin in normal amounts and this will cause clotting of hemophilic blood In this respect therefore there is no difference between the platelets of patients with hemophilia and those from a normal person unless it is in the rate in which the platelets give up the thromboplastin

One view held by Govaerts and Gratia (*199*) is that the apparent stability of the hemophilic platelets is due to the absence or deficiency of some constituent of the plasma According to them the inherited defect in hemophilia is an abnormality in the composition of the plasma which in some undiscovered manner acts in such a way as to cause the platelets to give up thromboplastin at a slower rate than normal Another view is that the platelets themselves are abnormal in that they give up the thromboplastin less readily This theory would place the defect in the platelets or in the megakaryocytes from which they are derived It has

study of other members of the family. It is possible, however, that sporadic cases may occur and hence mark the beginning of a new hemophilic strain. If this takes place, Howell (198) is of the opinion that it is a true hereditary condition which has arisen *de novo* by mutation of the sex cells of the mother.

In a group of 40 patients with hemophilia studied by Davidson and his associates (219) there were 28 with a family history of the disease. Of these, 25 had a known member of the family with the condition in the same generation. Fourteen were one generation back and four two generations. None were able to trace the condition further. The authors concluded that the lack of a history in some instances was due to incomplete knowledge of the family. There were, however, three patients in whom the history was known and in whose family there was no other person with hemophilia in the three previous generations. It is the opinion of Davidson and his associates (219) that these may represent instances of sporadic hemophilia. A more likely explanation, however, according to them is that the disease may be transmitted by the female through successive generations without manifestations in a male offspring. It is probably true, however, that spontaneous cases of hemophilia do arise. In some instances the family history is inadequate and in others the possibility of illegitimacy must be kept in mind. A remarkable instance of six cases in brothers with the disease whose family history gave no evidence of bleeders is reported by Boggs (220). Although the history of four generations on the mother's side is known, the legitimacy of the mother was questioned.

Hemophiliacs have no special constitutional makeup, although Birch (197) states that most of them have a scarcity of hair over the body. They may be of English, Spanish, Russian, Hebrew, Irish, Italian, Polish, Negro (Mulatto), German, Austrian, Belgian, Swedish stock, and perhaps also of other nationalities.

Does Hemophilia Occur in the Female?—It has never been established that true hemophilia has appeared in the female, although this is theoretically possible if a hemophilic male married a conductor female, for then there would be equal chance for the daughters to be conductors or active hemophiliacs. There is no authentic example of this recorded in the literature, however, for the cases reported probably had either pseudohemophilia, in which the bleeding time but not the clotting time is increased, or the bleeding was purpuric in nature, with or without thrombopenia. Support to the theoretical conclusion that hemophilia may occur in a female if a hemophilic male married a female conductor is supplied by breeding experiments in dogs which have been discussed previously (see page 581).

According to Madison and Quick (221) a number of cases of abnormal bleeding have been reported to occur in the female which closely simulate the clinical picture of hemophilia and have had the characteristic delay

females are mated with normal males the actual distribution into the four genotypes, namely normal females, transmitter females normal males and hemophilic males is approximately what would be anticipated (*213*) Furthermore it is of great interest to note that when a hemophilic male is mated with a transmitter female it is possible to demonstrate that the condition can occur in the female animal (*213*) This is what would be anticipated as both gametes may provide an affected X chromosome Such an observation is of great interest since in the past there has been a great deal of discussion concerning the possibility of the occurrence of active hemophilia in the female

A hemophiliac like disease occurs in swine (*214 215*) but it is not true hemophilia as it is not sex linked and active bleeders occur only when a female carrier is mated with a male carrier Apparently it is not possible to breed an active bleeder by mating a hemophilia carrier with a normal animal, irrespective of sex

Incidence —The actual incidence of the disease is not known but one is safe in stating that the condition is relatively uncommon although perhaps not as rare as previously supposed It is stated by Andreassen (*216*) that in Denmark it occurs at a rate of 81 hemophiliacs in a male population of 1 82 millions which would give an incidence of about 4 5 persons with the disease in 100 000 males It is estimated by Brinkhous (*212*) since hemophiliacs survive only about one third to one fourth as long as normal males that the frequency is approximately 13 5 to 18 0 hemophiliacs per 100 000 live male births The data collected in Skold in Sweden (*217*) gives the somewhat lower incidence of 3 1 per 100 000 live Swedish males or about 9 3 to 12 3 per 100 000 live births It is estimated by Brinkhous (*212*) that if these figures are applied to the United States a minimum of 2300 to 3300 cases exist in this country Quick (*218*) estimates that the disease occurs in about 10 per 100 000 males in Milwaukee

The Role of Heredity —It has been clearly established that the condition is hereditary and may be transmitted through many generations by females although the active disease appears only in males It is now generally agreed that the disease behaves as a sex linked mendelian recessive factor Studies have shown that a hemophilic male when married to a normal female never has hemophilic sons nor will any of the latter s sons suffer with the disease On the other hand, the disease may be passed on to future generations by the normal female s daughters whose sons may have hemophilia and whose daughters may continue to act as conductors and continue to pass the disease on to future generations

Although it has been clearly established that hemophilia is an hereditary disease there have been cases in which the hereditary trend cannot be demonstrated The explanation of this may be that the condition was not true hemophilia or that sufficient care had not been taken in the

marrow naked megakaryocyte nuclei were observed in the lung and kidney capillaries indicating that they were embolic

Symptoms and Signs —In infancy and early childhood there is nothing abnormal about the appearance of a child with hemophilia unless there has been crippling with hemarthrosis Mentally these children are normal or even precocious and usually are well adjusted to their misfortune In most instances they pass through each episode of bleeding with patience and fortitude It ■ undoubtedly true that the condition exists from birth but the clinical manifestations may not be apparent until some time later Birch states (197) that the initial hemorrhage occurs within the first three weeks of life in 25 per cent of the patients and that this most commonly arises following circumcision stretching of the fore skin or from the site at which the umbilical cord has been severed In 36 of the 40 patients studied by Davidson and his associates (219) the first evidence of abnormal bleeding occurred between the ages of one week and 13 years Three of these followed circumcision two at the age of one week and eight others had their initial bleeding during the first year of life Hence a total of 11 or almost one third of the patients had their initial evidence of an abnormal condition of the blood within the first year Of the remaining 25 patients 19 had their first bleeding episode before the age of five years In infancy and childhood the bleeding tendency most commonly manifests itself as hematoma of the head and knees from trauma bleeding from cut lips and occasionally from hemarthrosis Abnormal hemorrhage from primary dentition was observed by Davidson et al in only one of 22 patients in whom a history was available but it occurred in 12 of the 22 from secondary dentition

The outstanding manifestation of the disease is a constant tendency to bleed excessively from various parts of the body either following minor injuries or arising without the patient being conscious of having experienced trauma of any kind The most common sites of hemorrhage from which bleeding occurs in practically all patients are the subcutaneous tissues the muscles the joints and the teeth mouth gums and nose About one third of the patients have bleeding into the stomach intestine or peritoneum Rarely is hemorrhage observed in the central nervous system lung or pleura

Purpura is not observed characteristically as it is in patients with thrombocytopenic purpura It is true that ecchymoses and hematoma do occur but they usually follow known trauma Rarely do ecchymoses spread extensively but this tendency is observed in hematoma When severe injury occurs there may be extensive bleeding into the subcutaneous tissues which spreads along fascial planes Usually the extent of subcutaneous and intramuscular hematoma are much greater than they appear on the surface Hemorrhage into the gluteal muscles with a spread is one of the most common types of extensive muscular hemorrhages In some instances the bleeding may be so great that evidence of shock will ap

in coagulation time without other demonstrable hemostatic defects These authors define true hemophilia as a bleeding disease manifesting itself early in life occurring only in the male but being inherited through the female Until recently however the diagnosis of hemophilia has been uncertain and subject to serious error, consequently all cases which have not conformed to the classical definition must be viewed with reservation They report the case of a 30 year old married housewife in whom the bleeding time clot retraction time prothrombin concentration and platelet count were normal whereas the coagulation time was distinctly delayed (17 19 and 21 minutes on three different occasions by the Lee White method) The laboratory findings were similar to those in hemophilia in their patient except with respect to the clotting time of recalcified plasma It is known that oxalated hemophilic plasma when subjected to high centrifugation clots significantly slower on recalcification than that obtained by spontaneous sedimentation or slow centrifugation In marked contrast the plasma of this patient failed to show this striking difference due to centrifugation It is stated by Madison and Quick that the significance is not yet known, but Quick (222) has observed that such a test is consistently positive in a small series of cases with hemophilia and that it is negative in one or other of the atypical or hemophilia like conditions The patient reported by Madison and Quick had bleeding into the muscles intermittent hematuria and finally succumbed to bleeding in the base of the tongue Quick states (223) that in the condition described the coagulation defect seems to be the primary factor and suggests that the term hemophiloid be employed in describing such a condition

Pathology —The findings at necropsy are largely those due to hemorrhages and the immediate cause of death may be excessive loss of blood or pneumonia or more rarely hemorrhage into some internal organ The original observation has been made by Custer and Krumbhaar (224) that there is an increase in the megakaryocytes of the bone marrow in patients with this disease According to them observations in three patients with hemophilia one who died of hemorrhage another of infection and hemorrhage and a third of infection showed that there were approximately twice as many normal appearing megakaryocytes in the bone marrow of patients with hemophilia as in the non hemophilic controls

The only conditions found at necropsy which they consider worthy of comment were as follows no structural change of the blood vessels could be demonstrated the accessory blood forming organs namely the spleen and the lymph nodes showed no significant changes although an increased prominence of the cells of the reticulo endothelial system was noted in each instance there was no evidence for or against the formation of the megakaryocytes in any sites other than the bone

skin about the affected joint is not discolored but there is often a local and general increase in the body temperature The acute attacks persist for a few days to many weeks Repeated hemorrhages into the same joint result in permanent damage characterized by atrophy and proliferation of bone with roughening of the articular surfaces Konig in 1892 (*194*) gave the classical description of the three stage development of hemarthrosis in hemophiliacs as follows 1 bleeding into the joint or hemarthrosis 2 an inflammatory or panarthritis which is a non infectious process resembling somewhat joint tuberculosis and 3 the regressive stage followed by deformity and subsequent ankylosis It is recognized that hemorrhage along the epiphyseal line may interfere with the nutrition of bone and inhibit its growth There may be cyst formation with subsequent collapse and shortening of the bone Hemorrhage into the hip joint may lead to the destruction of the femur with resultant shortening of the leg

Although the ankle is usually the earliest joint involved the knee is most frequently the one which develops a permanent deformity The remaining joints in order of frequency to develop permanent deformity are the hips wrists shoulders small joints of the hands and feet and the vertebral articulations According to Birch (*197*) there may be severe acute hemorrhages into the maxillomandibular joint but never has she observed permanent deformity

The average patient with the disease usually develops joint changes within the first few years of life although in the milder cases this may be delayed until puberty or later In general it may be said that the higher grade deformities are associated with joint hemorrhages which appear early in life In the 98 cases of hemophilia observed by Birch (*197*) 83 had hemorrhages into the joints and in 66 there was permanent joint deformity

Treatment of Acute Hemophilic Hemarthrosis —It is properly emphasized by MacAusland and Gartland (229) that repeated hemorrhages into the joints of patients with hemophilia may cause the patient to become a wheel chair invalid In order to avert permanent joint deformity they propose the immediate treatment of such joint injury with hyaluronidase It is recommended that the joint be aspirated and a few cubic centimeters of fluid removed With the needle still in place 1000 turbidity reducing units of hyaluronidase mixed with 1 per cent procaine is instilled into the joint No attempt is made to move the joint for a 24 hour interval At the end of this time the bandage is removed and the joint inspected for residual distension and pain and for active and passive motion If significant signs and symptoms are present the injection is repeated Usually at the end of the second 24 hour period the results are satisfactory and full use of the joint is encouraged It is their opinion that hyaluronidase through its action on the ground substance of the synovial fluid and syno

pear and icterus an increased serum van den Bergh reaction reticulosis and urinobilinogenuria may be observed

Excessive bleeding from the mouth teeth gums and nose is exceedingly common and is often serious One of the first patients I observed with the disease almost bled to death from hemorrhage which arose as a result of biting his tongue He had a brother who died from hemorrhage following the extraction of a tooth The same patient whom I observed some years later had hemarthrosis of the elbow joint, the nature of which was unrecognized This led to an incision of the joint because it was thought that pus was present The eruption and loss of teeth are frequently accompanied by bleeding which persists for days or weeks unless the proper treatment is instituted promptly

Often the hemorrhage is greatly prolonged because the clot when formed is soft and bleeds with the slightest trauma The loss of blood may be tremendous and consequently there is a decrease in the blood volume with the development of a hypochromic anemia associated with a polymorphonuclear leukocytosis an increase in the blood platelets nucleated red blood cells and reticulocytes

Bleeding beneath the mucous membranes of the throat in the region of the pharynx and larynx may arise spontaneously or occasionally following excessive use of the voice and give rise to a dangerous hematoma formation This may threaten life by obstruction of the airway One patient in the group of 40 studied by Davidson and his associates (219) succumbed to this complication Seven instances of this serious complication have been collected and reported by Baird and Fox (225) In four of the cases tracheotomy was not done and all patients recovered whereas in three death followed the operation in their own case however recovery followed tracheotomy

Complications in the Lungs and Pleura —I have never observed bleeding into the lungs or involving the pleura and although rare it does occur Roentgen ray changes in the mediastinum and pleura have been reported (226) apparently arising from hematomata It is uncommon to observe massive hemothorax or hemoptysis (227)

Bleeding into the Central Nervous System —It is usually rare to have bleeding into the central nervous system although hemorrhage may occur into the brain or spinal cord This is in contrast to the comparative frequency of cerebral hemorrhage in thrombocytopenic purpura (228) Occasionally it has been observed that a retroperitoneal hemorrhage is of such an extent that it causes pressure on a nerve root where it emerges from the spinal column and causes unilateral radicular pain (219)

Hemarthrosis —In almost all patients with hemophilia there is bleeding into the joints which either arises from slight trauma or spontaneously As a result of the bleeding there is a swelling pain and increased tenderness about the joint Usually it is held in the position of flexion as this provides the least tension on the capsule and lessens the discomfort The

skin about the affected joint is not discolored but there is often a local and general increase in the body temperature The acute attacks persist for a few days to many weeks Repeated hemorrhages into the same joint result in permanent damage characterized by atrophy and proliferation of bone with roughening of the articular surfaces König in 1892 (194) gave the classical description of the three stage development of hemarthrosis in hemophiliacs as follows 1 bleeding into the joint or hemarthrosis 2 an inflammatory or panarthritis which is a non infectious process resembling somewhat joint tuberculosis and 3 the regressive stage followed by deformity and subsequent ankylosis It is recognized that hemorrhage along the epiphyseal line may interfere with the nutrition of bone and inhibit its growth There may be cyst formation with subsequent collapse and shortening of the bone Hemorrhage into the hip joint may lead to the destruction of the femur with resultant shortening of the leg

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vial membrane allows the reabsorption of the joint hemorrhage with resulting elimination of pain and permits early joint motion Certainly this method of management appears promising and should be carefully considered in all patients with this complication

Hematuria —Blood in the urine occurs at intervals in about one half of the patients with the disease If not from the bladder it may be from the kidneys and appear from one or both ureters This usually continues for a period of two to three weeks Some patients may simulate renal colic although it is usually not as severe as when a stone is passed Care should be used in instrumentation of these patients as such procedures are usually followed by a great increase in the loss of blood

Gastro intestinal Bleeding —Hematemesis or bleeding from the rectum occurs in about one third of all patients with the disorder It may be accompanied by abdominal pain distension increased peristalsis, fever and a leukocytosis In some instances intraperitoneal hemorrhage occurs in the right lower quadrant which may stimulate an acute abdominal condition Almost complete exsanguination may result from an intraperitoneal hemorrhage without the loss of a drop of blood externally

It is exceedingly rare to have bleeding into the central nervous system although hemorrhage may occur in either the brain or the spinal cord Rarely is there bleeding into the pleura or the parenchyma of the lung

Acute Abdominal Symptoms and Signs in Patients with Hemophilia — Occasionally a patient with known hemophilia may develop either severe colicky or steady abdominal pain muscular rigidity abdominal distension, nausea and vomiting moderate fever and leukocytosis These are signs of an important complication but the cause may be difficult to determine It may be due solely to bleeding into the abdominal cavity in patients with hemophilia or it may be associated with the condition which commonly causes such manifestations in otherwise normal persons, namely, acute appendicitis acute cholecystitis perforated peptic ulcer and other syndromes which are commonly regarded as acute surgical emergencies It is often difficult to determine the site of the bleeding if present in hemophilic patients It may be retroperitoneal into the wall of the small intestine or colon or the mesentery The signs in the latter conditions are usually those commonly associated with partial bowel obstruction

Retroperitoneal hemorrhage is not such a rare complication in patients with hemophilia In 15 of the 40 patients observed by Davidson and his associates there was one episode of iliopsoas hemorrhage (219), indicating that it is not an uncommon complication This condition has been described by Birch (230) and others (231 232) When on the right side, the condition may resemble acute appendicitis with severe pain extreme tenderness to palpation and percussion over McBurney's point and rebound tenderness

The situation presented by these acute manifestations possibly requiring surgical intervention in a patient with hemophilia is a complicated problem and one requiring great care and observation before resorting to surgery If the condition is due to hemorrhage and an operation is performed the result may be fatal as the operative mortality is high (233)

Changes in the Blood —The only characteristic finding in the blood of patients with hemophilia is the prolonged coagulation time and in general it may be said that the longer it is the more severe is the hemophilia There are however some exceptions to this In the mild cases the coagulation time varies between one half and one hour in the moderately severe cases from two to five hours and in severe cases from 15 to 24 hours When the clot does form it contracts and expresses serum normally It is characteristic for the clotting time to vary spontaneously within wide ranges According to Birch (197) the highest clotting time occurs in the early spring It should be kept in mind that rough handling of the blood shortens the clotting time In judging the effect of various types of therapy these factors should be taken into account

The bleeding time as determined by the Duke method, in patients with hemophilia is almost always normal but it may be increased in patients in whom the coagulation time is also prolonged For example Birch (197) cites a case in whom the coagulation time was 22 hours and the bleeding time was 48 hours In general however it can be said that the bleeding time is increased in less than 10 per cent of the patients and this occurs only when the coagulation time is 10 hours or more Usually the tissue juices contain a sufficient quantity of thromboplastin to cause the bleeding time to be normal This also explains why bleeding from small cuts in patients with the disorder is rarely important

The clotting time of recalcified plasma the prothrombin consumption test, and testing the coagulating effect of normal on hemophiliac plasma and the latter s effect on plasma from known hemophiliacs are discussed on page 591

The hemoglobin and red blood cell count may be normal or reduced depending on the extent of the hemorrhages in any given patient In prolonged and extensive hemorrhages the latter may be below 1 0 million per cubic millimeter and the hemoglobin below 20 per cent. With chronic bleeding the anemia is of the microcytic hypochromic type but with acute bleeding it may be for a short interval of the normochromic macrocytic type

The leukocytes are normal in all respects except following acute bleeding when there is usually a polymorphonuclear increase with an excessive number of young white blood cells ("shift to the left") Also the platelets are normal in number and appearance although it is thought by some that they are abnormally resistant Never in my experience have they been reduced The blood calcium antithrombin fibrinogen and hydrogen ion concentration are normal

Diagnosis —There are three diagnostic features of hemophilia which are ordinarily readily determined and therefore, usually make recognition of the disease relatively easy They are 1, the history of repeated episodes of excessive bleeding in males beginning early in life, 2 the demonstration that the coagulation time of blood is prolonged often to a pronounced degree, usually without changes in the bleeding time prothrombin concentration calcium concentration, platelet count capillary fragility, or clot retraction and 3 a history which indicates that the disease is hereditary and sex linked The first two features must be present before the diagnosis can be made The third is confirmatory but not absolutely essential to the diagnosis To determine this accurately it is necessary to obtain a rather extensive family history which is not possible in some cases and the condition may not be present in all generations It should also be kept in mind that illegitimacy may be a source of error in the family history Furthermore as previously mentioned according to Howell (*198*) there is evidence which indicates that sporadic cases do occur in which inheritance cannot be demonstrated These he suggests may arise *de novo* by mutation of the sex cells of the mother and hence would mark the beginning of a new hemophilic strain

The following changes are of value in determining the diagnosis of the disease

1 The coagulation time as determined by the technic of Lee and White is always prolonged although in some patients for long intervals the prolongation may be slight This differentiates hemophilia from pseudohemophilia the purpuras, and scurvy

2 The bleeding time as performed by the method of Duke is almost always normal but may be increased in a few cases in which there is undue prolongation of the coagulation time (usually longer than 10 hours) A normal bleeding time differentiates hemophilia from the thrombopenic purpuras in which the clot retraction is abnormal

3 The tourniquet test This is almost always negative in patients with hemophilia but occasionally it may be present when the coagulation time is greatly prolonged Ordinarily it is considered to differentiate it from bleeding conditions in which there is increased permeability of the capillaries

4 The platelet count in hemophilia is always normal or it may be increased if there has been excessive bleeding It is never decreased The platelets are present in normal numbers in pseudohemophilia and in nonthrombocytopenic purpura but of course are diminished in number in the thrombopenic purpuras

5 Quick (*234*) has pointed out that in patients with hemophilia the coagulation time of recalcified plasma following high speed centrifugation is over five minutes and after low speed centrifugation is over three minutes He suggests this as a test for hemophilia which is based on the belief that the delayed coagulation in hemophilia is due to an abnormal

resistance of the platelets In hemophilic blood apparently due to the greater stability of the platelets very few of them undergo lysis Consequently when the blood is centrifuged at high speed the intact platelets are thrown down leaving the plasma poor in both liberated and potentially free thromboplastin *Hence the plasma so obtained clots less rapidly* With slow centrifugation many platelets remain in suspension and suffer disintegration incident to recalcification and hence clotting is *more rapid* In the opinion of Quick (*222*) the evident influence that centrifugation has on the coagulation time of hemophilic plasma in contrast to the slight effect on normal plasma offers a new test for the diagnosis of the disorder

It has also been shown by Quick (*234 201*) that the prothrombin consumption test is a measure of the amount of available thromboplastin in the blood Normally there is a sufficient quantity there to convert about 85 per cent of the prothrombin to thrombin When the prothrombin consumption test is incomplete it suggests either a deficiency of thromboplastin due to lack of platelets as in thrombocytopenic purpura or a deficiency of thromboplastinogen the precursor of thromboplastin as in hemophilia As Quick says (*234*) the prothrombin consumption varies considerably in normal persons In hemophilia and thrombocytopenic *purpura it is very incomplete indicating that there is a deficiency of* thromboplastin In hypoprothrombinemia the prothrombin consumption is complete as in the hypoprothrombinemia of the Component A type It is emphasized by Quick (*202*) however that the test is important clinically but it is not always a true quantitative measure of thromboplastinogen the name given to the precursor of thromboplastin Under carefully controlled conditions however according to Quick (*202*) and with an adequate supply of platelets nearly all of the thromboplastinogen becomes available thromboplastin

It has long been known that the addition of normal plasma to blood from patients with hemophilia will cause it to clot promptly Recently Goldstein and Alexander (*235*) have emphasized that the ability of normal plasma to reduce the clotting time to normal and also increase the *prothrombin consumption is fairly uniform On the other hand plasma* from patients with hemophilia has slight if any effect They suggest therefore that in patients suspected of having hemophilia their blood plasma be tested with respect to the ability to accelerate the clotting of known hemophiliac blood In outspoken cases with prolonged coagulation time this test is of course unnecessary but it is useful in patients with hemophilia when the clotting time is in the upper range of normal or only slightly elevated

In resume the blood of a patient with true hemophilia should show the following (*222*)

1 *Coagulation time (technic of Lee and White)* over eight minutes at 37 5 degrees centigrade

2 Coagulation time of recalcified plasma
 (a) High speed centrifugation over five minutes
 (b) Low speed centrifugation over three minutes
 (c) Clotting time should decrease on standing
3 Prothrombin concentration (Quick s method) above 70 per cent
4 Bleeding time (Duke s method), not over four minutes
5 Clot retraction not over 60 minutes after coagulation occurs
6 Tourniquet test (Rumpel Leede technic) not over four petechiae in any specified area
7 Incomplete utilization of thromboplastin as shown by the prothrombin consumption test
8 Effectiveness of normal plasma in causing prompt coagulation of hemophiliac blood and the latter s ineffectiveness in causing clotting of known hemophiliac blood

In a comprehensive article dealing with the diagnosis of hemophilia Quick and Hussey (*236*) state the diagnosis of the disorder cannot always be made on the triad of a bleeding tendency prolonged coagulation time and a positive family history They emphasize that there may not be a family history of male bleeders and in a mild type of hemophilia the coagulation time may be within the normal range although the latter has rarely occurred in my experience They observe however that the prothrombin consumption time is consistently positive except in the mild cases It is recommended that a new procedure named the thromboplastinogen activity test" be used This consists in adding heated rabbit brain extract to blood and determining the prothrombin of the resulting serum By this method a low consumption of prothrombin is found in even mild cases of hemophilia

Course of the Disease and Prognosis—About three fourths of the patients with severe hemophilia succumb before the age of 20 years Almost one half of the patients are classified as having the disease in the severe form as indicated by a coagulation time of between 18 and 22 hours There is abundant evidence to indicate that the severity of the disease parallels the length of the coagulation time These patients suffer with numerous spontaneous hemorrhages frequent joint complications and long periods of invalidism After the age of 20 years practically every patient with severe hemophilia has permanent joint deformity

In an analysis of the age at the time of death in 113 patients Birch (*197*) found that 35 per cent of the patients died within the first year This is three times the death rate of male infants in the registration area of the United States Further analysis shows that three of the patients died on the first day 20 within the next nine days six between the ages of 10 days and three months two between three and six months and nine between six months and a year During the second year five patients died six succumbed in the third year 11 in the fourth year and three in

the fifth year Altogether 57 per cent of the patients died in the first five years as compared with the normal rate of 15 per cent Birch (197) states further that 66 7 per cent of American male infants can be expected to survive beyond the fortieth year This is approximately one twelfth of the normal life expectancy

If a patient survives until the age of 20 years the outlook for many more years of life is much better As Birch (197) has emphasized this improved outlook is due to many factors as follows 1 those with the most severe forms of the disease do not survive to the age of 20 years 2 by this age the eruption of teeth which is one of the serious causes of bleeding is over 3 the exposure to trauma is less after childhood is passed 4 as the patients grow older more discretion and judgment are used in avoiding injury and 5 many patients are not subjected to injury because of the limitations of their activity on account of joint deformities

On the other hand as the individual grows older the joint deformities often become more pronounced with each hemorrhage which leaves the joints a little more damaged This is likely to progress until they are functionless

With the increased knowledge concerning the disease and the ease with which blood transfusions or dried plasma may be given it is likely that in the future the lives of these patients may be prolonged to a greater length

Cause of Death in Hemophilia—In an analysis of the causes of death in 113 patients with hemophilia Birch (197) has found that the most frequent one is exsanguination following surgical procedures In her series there were 25 of these 15 followed circumcision six were due to tooth extraction although the diagnosis was known in each instance before the tooth was extracted one resulted from tonsillectomy one from an incision of the throat the operation having been done to relieve pressure symptoms due to hemorrhage one was due to an incised hematoma of the scalp and one followed vaccination It is noted that this was the only hemorrhage following vaccination although all of the patients over seven years of age in her series had been vaccinated

In 23 patients a fatal hemorrhage occurred from small accidental cuts such as a cut lip from biting the tongue and trauma resulting in hemorrhages from the forehead finger leg and scalp

Internal hemorrhage was the cause of death in 21 cases Four of these occurred following trauma which could have been the cause of death in a normal person whereas three followed slight injury and in 14 cases the internal bleeding was apparently spontaneous

Other causes of death were as follows fatal epistaxis occurred in six cases cerebral hemorrhage in five hematuria in four hemorrhage from the umbilical cord in four hemorrhage from the lung in three (one dur

ing the course of pneumonia) There were three fatal cases of gastric hemorrhage, and three from the intestine of which one occurred during *the course of typhoid fever* Birth trauma was fatal in three (in two there was forceps delivery) Bleeding from the throat during the course of diphtheria occurred in three cases and hemorrhages in the spinal cord in two Pneumonia followed extensive bleeding in two cases The bleeding was due to instrumentation of the ear in one case and the other followed appendectomy

Two patients were said to have died of natural causes one associated with heart disease and the other from the complications of old age at 69 years One patient had a fatal hemorrhage following a fracture of a leg another had generalized subcutaneous hemorrhage and still another died of croup One bled to death from the gums following the eruption of a tooth

Of the 113 deaths Birch regards 106 as due to hemophilia and the other seven to natural causes

Treatment —It is too much to hope that this disease due to a hereditary defect in the blood can be cured permanently by any type of therapy The therapeutic efforts for the control of the condition should be directed toward 1 the injection of substances into the blood stream which will shorten the coagulation time 2 local treatment applied to bleeding sites in an effort to control bleeding 3 the management of such a patient if surgical measures become necessary 4 the avoidance as near as possible of trauma 5 the control of the condition by the regulation of marriage and pregnancy and 6 a consideration of measures to assist the patient in an adjustment to the social and psychiatric consequences of the disorder

General Care of the Patient —As stated elsewhere (see page 593), *almost all patients with hemophilia succumb to the disease* the most common cause being hemorrhage following surgical procedures Next in frequency is exsanguination as a result of small accidental cuts and from *trauma of the forehead fingers legs and scalp* Strict precautions should be taken by the hemophiliac to prevent such accidents although the physician should be careful not to overemphasize this phase of the treatment lest unnecessary psychic trauma be inflicted upon the patient In other words the patient should not lead a life which is too protected and inactive but should avoid all strenuous exercise and dangerous physical hazards *in order not to cause bleeding* Excessive fatigue should be avoided and at least eight and preferably nine hours rest out of each day should be obtained He should therefore be fully informed of his *condition*

It would be advisable if he carried with him especially if going into more isolated communities a preparation of thrombin for local application Likewise he should know his blood group and if he is Rh positive

or negative If these facts are presented to him in the proper way it will provide reassurance and tend to dispel his fear rather than augment it Furthermore he should be told that blood and plasma are now available almost universally and therefore the proper treatment has been made accessible whereas heretofore it could be obtained only in certain communities

The Use of Blood, Plasma, and Plasma Fractions Intravenously —The most effective treatment of excessive bleeding in a patient with hemophilia is the intravenous injection of fresh citrated whole blood or plasma It has been my custom to use blood or plasma that is not over 24 hours old and Davidson and his associates (*219*) and Goldstein and Alexander (*235*) concur with this policy It is of interest to note however that the investigations of Taylor and his associates in 1944 (*237*) demonstrated conclusively that the anti hemophilic component of plasma is remarkably well preserved in both liquid and frozen plasma In fact they found that full potency of the antihemophilic substance remained in liquid plasma at the end of six months when the material was left at room temperature The prothrombin content of this liquid however was practically absent

When a sufficient amount of blood has been lost to produce an anemia the treatment of choice is whole blood in amounts of 500 cc repeated as often as necessary to control the anemia Such transfusions not only reduce the clotting time to normal promptly but also raise the hemoglobin and red blood cell count to their proper levels Plasma fresh frozen or dried provided too long a period has not transpired after it is withdrawn from the donor is potent and easier to give as cross matching is not necessary This may be used if there is no indication that the loss of blood has caused an anemia

Whole blood should be given every eight to 12 hours in amounts sufficient to bring the hemoglobin and erythrocyte count to normal as well as to control the clotting time Plasma may be administered in amounts varying from 100 to 250 cc at the same time intervals

Within 15 to 30 minutes after the injection of either whole blood or plasma there is a sharp fall in the clotting time to the vicinity of normal usually below 20 minutes where it remains for six to 12 hours It then gradually rises in the next six to 12 hours to the preinjection level (238)

If the bleeding is not controlled by intermittent intravenous injections of whole blood or plasma then the possibility of giving plasma 300 cc or blood 600 cc diluted to 2000 cc with normal saline by continuous intravenous drip should be considered This method of treatment has been used successfully by Aggeler and Lucia (239) In my opinion under no circumstances should blood or plasma be given intramuscularly

It is probably optimum therapy in most of the cases to give 100 to 250 cc of plasma intravenously once or twice daily although in some patients

ing the course of pneumonia) There were three fatal cases of gastric hemorrhage and three from the intestine of which one occurred during the course of typhoid fever Birth trauma was fatal in three (in two there was forceps delivery) Bleeding from the throat during the course of diphtheria occurred in three cases and hemorrhages in the spinal cord in two Pneumonia followed extensive bleeding in two cases The bleeding was due to instrumentation of the ear in one case and the other followed appendectomy

Two patients were said to have died of natural causes, one associated with heart disease and the other from the complications of old age at 69 years One patient had a fatal hemorrhage following a fracture of a leg another had generalized subcutaneous hemorrhage and still another died of croup One bled to death from the gums following the eruption of a tooth

Of the 113 deaths, Birch regards 106 as due to hemophilia and the other seven to natural causes

Treatment—It is too much to hope that this disease due to a hereditary defect in the blood can be cured permanently by any type of therapy The therapeutic efforts for the control of the condition should be directed toward 1 the injection of substances into the blood stream which will shorten the coagulation time 2 local treatment applied to bleeding sites in an effort to control bleeding 3 the management of such a patient if surgical measures become necessary 4 the avoidance as near as possible of trauma 5 the control of the condition by the regulation of marriage and pregnancy and 6 a consideration of measures to assist the patient in an adjustment to the social and psychiatric consequences of the disorder

General Care of the Patient—As stated elsewhere (see page 593) almost all patients with hemophilia succumb to the disease the most common cause being hemorrhage following surgical procedures Next in frequency is exsanguination as a result of small accidental cuts and from trauma of the forehead fingers legs and scalp Strict precautions should be taken by the hemophiliac to prevent such accidents although the physician should be careful not to overemphasize this phase of the treatment lest unnecessary psychic trauma be inflicted upon the patient In other words the patient should not lead a life which is too protected and inactive but should avoid all strenuous exercise and dangerous physical hazards in order not to cause bleeding Excessive fatigue should be avoided and at least eight and preferably nine hours rest out of each day should be obtained He should therefore be fully informed of his condition

It would be advisable if he carried with him especially if going into more isolated communities a preparation of thrombin for local application Likewise he should know his blood group and if he is Rh positive

not over 24 hours old In the case of lyophilized plasma which is known to be active there is a certain risk that it may not be potent because it may not be processed for some time after it has been drawn and in this interval there may possibly be an appreciable diminution in its anti hemophilic activity If a significant anemia is not present then fresh plasma or that which has been separated soon after it is removed from the donor and preserved in the frozen state may be used A satisfactory dosage of plasma is 100 to 250 cc once or twice daily depending on the change in the coagulation time and is usually adequate during active bleeding In some patients however it may be advisable to give 100 cc of plasma every eight hours

Recently Van Creveld and Paulssen (*241*) have reported that the use of plasma in which heparin has been used for its anticoagulant properties has greater and more lasting benefit than transfusions with citrated plasma They observed a patient with hemophilia in whom the citrated plasma had a gradually diminishing effect It was their conclusion that there is a possibility of a less favorable effect of citrate on some factors of coagulation which may disappear if the citrated plasma is given less frequently Based on an experience of three years they conclude that heparinized plasma does not have the same disadvantage In a patient with hemophilia who had a circulating anticoagulant the transfusions of heparinized plasma were unable to shorten the coagulation time importantly This work suggests that patients with hemophilia who eventually react less favorably to citrated plasma transfusions should be given a trial of transfusions with heparinized plasma provided a circulating anticoagulant is not present

The Control of Bleeding Following Surgical Procedures —Although a mortality rate as high as 35 per cent has been reported in patients with hemophilia who have been operated upon (*242*) major procedures have been performed successfully Reports of the following operations have been collected from the literature by Davidson *et al* (*219*) appendectomy gastroenterostomy partial gastrectomy arthroplasty eye enucleation prostectomy nephrectomy mastectomy and various amputations

Even minor surgical operations should not be carried out in these patients without careful preparation When such operations are necessary it is possible to protect a patient by means of blood transfusions which will temporarily reduce the coagulation time to normal According to Jones and Tocantins (243) improvement in the clotting time usually persists for two to six days In each case blood transfusions should be given until the clotting time is reduced to normal if this is possible Certainly no operative procedure unless extreme urgency exists should be done until the coagulation time is below 20 minutes Frequent checks of the coagulation time should be done following the operation and transfusions repeated as indicated

it may be necessary to give 100 cc every eight hours. The difference in dosage is because it is known that a patient with hemophilia differs from time to time in his response to antihemophilic material of known potency.

It has been observed by Johnson (240) that lyophile human plasma when injected intravenously in amounts varying from 125 cc to 150 cc decreases the coagulation time in hemophilia. This indicates that freezing and drying of the plasma within a few hours after it is removed from the donor does not destroy the activity of the effective material in blood plasma. This observer has employed lyophile plasma in the management of hemarthrosis, hematuria and tooth extractions, and as a prophylactic agent against recurrent hemorrhages in patients with the disorder. In all of these conditions this form of therapy has produced most gratifying results. It is effective in the control of hemorrhage following the extraction of teeth when carried out according to the following plan (240): 150 cc of plasma is given prior to the extraction; immediately after the teeth are removed the sockets are packed with dry plasma. During the next few days plasma is given daily in amounts necessary to keep the coagulation time at 20 minutes or less, as it has been observed that excessive bleeding is likely if the coagulation time exceeds this figure. In one patient Johnson (240) gave weekly injections of 125 cc of plasma for three months. With this dosage the coagulation time, which had previously been in the vicinity of 100 minutes, promptly dropped to near normal in the first 24 hours and gradually increased to 60 minutes at the end of six days. During the greater portion of the time the patient was completely free from bleeding. He believes that the intensive treatment of incipient hemorrhages with plasma is the most practical method available for the rehabilitation of patients suffering from the disease.

With the demonstration of the *antihemophilic activity of fraction I* of Cohn (236), it was the hope that this substance might prove to be the ideal form of therapy in patients with hemophilia. While it will promptly cause a shortening in the clotting time, it is not the treatment of choice at present. This is for three main reasons, as follows: 1. it is not commercially available at present; 2. although it was first thought incapable of transmitting hepatitis, it is now known to do so (219); and 3. finally, it may be responsible for the development of a refractory state, perhaps as the result of the production of antibodies, which nullifies its beneficial effects. A statement concerning the possibility of the latter deleterious effects is made by Davidson and his associates (219) as follows: "presently available evidence suggests that this refractory state may occur more frequently following the administration of the antihemophilic globulin fraction than following the administration of blood or blood plasma. The therapeutic use of the antiglobulin fraction cannot be advised, therefore, until further studies have eliminated this hazard."

In summary, therefore, the immediate control of bleeding is best accomplished by the injection of 500 to 600 cc fresh whole citrated blood

the results were inconsistent and in his opinion they were undoubtedly due to spontaneous changes in the coagulation of the blood or to minor differences in the technic of sampling

The claims that other forms of treatment are effective have not been substantiated Birch (250) in 1931 reported that she had treated cases successfully with ovarian extract but this has not been confirmed and it is no longer recommended

Oxalic acid as a form of therapy to increase the coagulation of the blood was introduced by Steinberg and Brown (251) and favorable reports have appeared indicating its effectiveness in the treatment of bleeding due to hemophilia In a careful study (252) of five patients with hemophilia who were given oxalic acid in doses varying from 10 to 47 milligrams daily there was no reduction in the coagulation time although a prompt fall occurred when lyophile plasma or citrated blood was administered It would seem therefore that oxalic acid therapy is of uncertain value in the treatment of hemorrhage associated with this disease

Prophylactic Treatment with Plasma Transfusions—Theoretically it appears worth while to plan some type of treatment whereby if possible the coagulation time is kept at or near a normal level in an attempt to prevent bleeding of all types including the disabling hemorrhages into the joints Such a program has been carried out by Alexander and Landwehr (253) They maintained a regimen of plasma infusions on five patients with hemophilia given injections at least three times weekly over a period of one to five years They reported that the incidence of hemorrhage was much less bleeding episodes when present were not so severe hospital admissions were reduced and the patients were able to undertake greater physical activities and live a more nearly normal life Consequently the patients have less fear of impending hemorrhage

These patients were treated with plasma alone and no evidence of refractoriness to it developed These observers point out that where refractoriness has been described in the literature (254) eight of the nine subjects had received Fraction I in addition to blood or plasma This infers that possibly refractoriness to blood or plasma alone given according to this plan is unlikely to occur

My present advice is to recommend a more conservative policy and give treatment only when specific indications arise Additional experience may alter this

Refractoriness in Hemophilia to Coagulation—Promoting Agents—In 1943 Monroe and Jones (255) reported that a patient with hemophilia apparently developed a resistance to transfusions with whole blood and plasma These forms of therapy eventually proved to be actually detrimental rather than beneficial to the patient When this occurred these observers determined that this patient had developed a circulating anticoagulant in association with the gamma globulin fraction of the plasma proteins

In the cases of abdominal operations electrosurgery may be employed Custer and Krumbhaar (*224*) report the case of an 11 year old patient with hemophilia in whom an exploratory laparotomy was done on the basis that the patient might have had an acute appendicitis This was accomplished by means of the Bovie knife with no operative hemorrhage In this patient it was found that the abdominal symptoms were due to retroperitoneal hemorrhage which may simulate an acute condition of the abdomen requiring operation

With the proper preparation by means of blood transfusions, and especially if electrosurgery is employed it is possible therefore to perform safely almost any type of urgent surgery Reference should be made to page 597 for details of controlling bleeding by human blood plasma following tooth extraction

Local Treatment to Bleeding Sites—Ordinarily there is no important bleeding from minor injuries to the skin as usually there is a sufficient admixture of the tissue juices containing thromboplastin to control oozing from the capillaries In other wounds the usual surgical methods should be employed, and in addition blood or plasma transfusions should be given and some type of freshly prepared tissue extracts should be applied locally According to Howell (*244*) a glycerine extract of dried lung provides an unusually potent preparation for local use and the potency is retained for a considerable period of time with refrigeration Beef globulin (*245*) placenta (*246*), and coagulating snake venoms (*247*) have been recommended but the potency of some of these preparations on the market varies considerably It is sometimes effective to apply a sponge soaked in normal human plasma or human blood after first cleansing the wound in order to permit the thromboplastin contained in such material to come in direct contact with the bleeding surfaces

Excellent results have been reported by the use of thrombin (*219*) when applied directly to the source of bleeding The material which is used for this purpose may be made from animal (*248*) or from human blood (*249*) Thrombin for topical use made from bovine plasma is now available commercially

It is not recommended that cauterizing material or the actual cautery be used While this form of treatment may stop the flow of blood temporarily it destroys tissue with a subsequent slough and additional bleeding

Oral Therapy of Hemophilia—According to Howell (*198*), it is apparently impossible to affect the coagulation time of the blood by the administration of anything by mouth and absorption from the alimentary canal This observer has listed a large group of substances which he has tried without effect and apparently he has little if any hope of producing promising results by this method of therapy In some instances, following oral therapy he observed slight changes in the coagulation time but

These psychic influences combined with the demeanor of an oversolicitous mother stimulated by a feeling of guilt and sometimes by the action of a father who harbors a subconscious resentfulness makes a situation which provides an ample basis for pronounced emotional instability in the patient. The matter is well summarized by the statement of Goldstein and Alexander (235) who say "These aspects of the disease together with the many necessary hospital admissions and their attendant cost the difficult domestic and school situation the difficulties created by a chronic crippling disorder with unpredictable acute episodes and the need for vocational guidance and rehabilitation pose problems which require great skill thought and cooperation on the part of both the physician and social worker"

Great insight sympathetic understanding tact and a willingness on the part of the physician to devote a considerable amount of time to the patient is necessary in order to be of real assistance. He can be reassured that better methods of treatment now make the disease less hazardous. An attempt should be made to inure him tactfully to the nature of the problem which confronts him. He should be urged to meet it in a way which will be most profitable to him. In some patients the process of sublimation may be skillfully employed to spur them on to greater attempts to acquire as normal a mental status as possible. All efforts should be made to train them early in life in such a way that they will not become dependent but will be able to earn their own living.

The problem of marriage and having children is an important psychiatric aspect of the condition. If such a union is forbidden this may play an important psychic role in the mind of the patient. On the other hand if such a patient does become married the possibility of transmitting the disease must be given serious consideration. The only persons of a hemophiliac family who can marry and have children without fear of transmitting the disease are the unaffected sons of a father with the disease. If a male hemophiliac marries a normal female none of the sons will be bleeders. The daughters however may be transmitters so that the male grandchildren of such a marriage may be hemophiliacs. A female carrier will transmit the trait to one half of her daughters who may be responsible for the active disease in any of their sons. Unfortunately there is no way a female carrier can be identified except by giving birth to a hemophiliac son. It is reported by Davidson and his associates (219) that 10 of 28 hemophiliacs whom they observed over 20 years of age were married and had 13 children.

The physician assumes a heavy responsibility when he advises against marriage in these patients. By so doing he may be adding a further psychic trauma to a life which already has more than its share. Needless to say the situation should be explained fully to both prospective par

Recently studies have been reported by van Creveld Hoorweg and Paulssen (256) of a circulating anticoagulant in the blood of a patient who became refractory to whole blood plasma and plasma fractions which developed after 30 blood transfusions had been given. They determined by fractionation of the plasma that the anticoagulant was associated with the pseudoglobulin fraction of the plasma. In their opinion it produced its effect by inhibiting the action of the antihemophilic globulin present in normal blood. The antihemophilic globulin however was not physically altered by the anticoagulant and could be reprecipitated without loss of its antihemophilic properties. They observed that the anticoagulant did not inhibit prothrombin, thromboplastin, or fibrinogen. It was not related to the lipid antithromboplastin or to heparin and did not appear to be an antibody. Subsequent studies dealing with this aspect of the treatment of hemophilia have been made by other observers (257 258 259)

In a careful study of 22 patients with classic hemophilia, it was found by Frommeyer Epstein and Taylor (254) that five patients developed clinical and laboratory evidence of refractoriness to therapy. In all instances this followed the intravenous injection of large amounts of plasma fractions in addition to whole blood and plasma. It is their conclusion that a refractory state may develop in such patients following the therapeutic use of whole blood plasma or prepared plasma fractions. They interpret this development as apparently an immune response which nullifies the usual beneficial effect of normal blood and plasma derivatives usually employed as therapy. It was determined that this refractory state can be promptly, but only temporarily abolished by the transfusions of very large amounts of fresh whole blood. In view of their findings it is the opinion of Frommeyer Epstein and Taylor (254) that whole blood plasma and chemically prepared plasma fractions should be withheld in the treatment of hemophilia unless their employment as an emergency measure is necessary.

The Psychiatric and Social Aspects of Hemophilia—It is amazing that scant attention has been devoted to the disease by the psychiatrists when one considers that this aspect of the disorder may be such a prominent one. Perhaps it is because the condition is relatively rare although recent figures indicate that it occurs more frequently than had previously been supposed. Eventually the patient learns in every case its precise nature and all of its handicaps. Then depending largely on his own inherent personality and the advice given he reacts accordingly. All patients invariably become acquainted with the seriousness of the disorder its permanency and unpredictability the lack of a cure the risk to their lives and the great possibility of becoming crippled, often extensively. They soon become aware of its hereditary nature the hazard of transmitting it and of the possibility that their daughters may become carriers and their grandsons victims of the disease

addition Glanzmann (*260*) produced coagulation in the normal platelet free plasma by the addition of platelets for one of his cases These observations suggest that there are no abnormalities in the blood platelets from a qualitative as well as from a quantitative standpoint as has been previously claimed

It is the opinion of Estren Sanchez Medal and Dameshek (*262*) that this disorder is due to an abnormality of the vascular apparatus Or as they state it is a form of nonthrombocytopenic vascular purpura in which a hitherto undemonstrated defect of the capillary system is present This capillary defect was originally described by MacFarlane (*268*) and consists of a disturbance in contractility

Clinical Manifestations —The disease is characterized by abnormal bleeding especially from the gums the nose and into the skin and subcutaneous tissues following slight trauma Loss of blood however may occur from almost any part of the body and hence there may be gastro intestinal hemorrhage with the vomiting of blood and tarry stools gross hematuria hemoptysis menorrhagia and metorrhagia and hemarthrosis Occasionally there are petechiae on the skin and mucous membranes and in rare instances hematomas

The other common clinical manifestations are related to the anemia which is of the microcytic hypochromic types and is accounted for entirely by the repeated hemorrhages As the bleeding is often severe there may be intense pallor ease of fatigue weakness dyspnea and palpitation which are directly referable to the pronounced reduction in the hemoglobin of the circulating blood and the red blood cell count In some instances it has been reported that the spleen is palpable just below the costal margin It has also been observed that the heart is moderately enlarged with an associated systolic murmur of a hemic variety The cardiac hypertrophy may be accounted for on the basis of the pronounced anemia over a long period of time which places an added burden on the heart as it does in other chronic anemias as for example the sickle cell type in which there is also cardiac enlargement

Blood Examination —The characteristic findings in the blood are 1 a prolonged bleeding time which usually exceeds 20 minutes and may be much longer 2 a normal number of platelets and 3 a normal coagulation time The results of the tourniquet test the prothrombin time and the clot retractility vary from time to time in the same patient and also in different patients These are normal in most cases

The only other abnormality found in the blood is the presence of a microcytic hypochromic anemia Its severity fluctuates considerably but the hemoglobin is usually between 50 to 80 per cent and the red blood cell count between 3 0 and 4 0 million per cubic millimeter In one case (*269*) the hemoglobin was recorded as 9 *per cent* and the red blood cell count as 1 370 000 per cubic millimeter Bleeding is so severe as to cause death in some patients In one of my recent patients

ticipants to the union They should then make their own decision and accept full responsibility for their action

HEREDITARY PSEUDOHEMOPHILIA

Synonyms—Hereditary hemorrhagic thrombasthenia (Glanzmann *260*) constitutional thrombopathy (von Willebrand *261*) familial purpura

Definition—A chronic familial hemorrhagic state which occurs in both sexes and may be transmitted by either parent It is characterized by a prolonged bleeding time with a normal platelet count, coagulation time and clot retractility

In an extensive review of the subject and an analysis of eleven of their own patients Estren Sanchez Medal and Dameshek (*262*) conclude that there is a *hemorrhagic disorder characterized by a tendency to bleed in the presence of normal platelets, a normal coagulation time and an increased bleeding time* They believe that the term pseudohemophilia should be restricted to those cases as defined above In the distant past however they state it was the tendency to classify as pseudohemophilia any bleeding disease which was not hemophilia There is a difference of opinion, however concerning this as MacFarlane (*263*) proposes that the designation pseudohemophilia be restricted to that state in which there is a clotting defect indistinguishable from that found in hemophilia but which could not be regarded as such for genetic reasons

Etiology—It is likely that Glanzmann's cases of "thrombasthenia (*260*) and those of von Willebrand's (*261*) ("pseudohemophilia" constitutional thrombopathy) should be included in this group

This condition is seen both in males and females As the clotting time is normal it differs definitely from hemophilia Although the bleeding time is prolonged the blood platelets are present in normal numbers and hence it is not the same condition as thrombopenic purpura

It has been determined by von Willebrand (*261 264*) that the disorder *is transmitted as a dominant sex linked mendelian characteristic* Studies of affected families show that it may be transmitted directly by the males through four generations of a family Buckman (*265*) and Giffin (*266*) each record a case in which the condition was transferred through four generations by females An extensive study of a family was made by Farber (*267*) who found that 14 males and 11 females were affected in 100 members of five generations

The exact cause of the condition is unknown but it has been ascribed to functional deficiency in the blood platelets This is not however supported by the observations of Buckman (*265*) in which he added a suspension of platelets from the blood of his patient with the disease to blood from a patient with hemophilia and noted that coagulation was produced as rapidly as with platelets obtained from normal blood In

amount of the patient's blood to normal blood and demonstrating that coagulation is prolonged. This test may be performed effectively according to the simple technic of Singer, Mond, Hyman, and Levy (271). The latter are of the opinion that the anticoagulant acts by interfering in some manner with the formation of thromboplastin although some antiplastic activity could not be excluded.

A review of the literature is given and a case of this disorder reported in a 30 year old Jewish female by Dreskin and Rosenthal (273). The patient first came for examination on account of hematoma and ecchymosis formation. The coagulation time was 39.5 minutes (Lee White), bleeding time (Duke) two minutes, prothrombin time normal, platelets normal, fibrinogen 0.3 gram per cent, clot retraction normal, the tourniquet test positive. A circulating anticoagulant was demonstrated by adding small amounts of plasma from the patient to normal blood thereby producing a delay in the clotting of normal blood. Treatment was given with protamine, fraction I (antihemophilic) globulin, whole blood, fresh serum, but none shortened the prolonged coagulation time consistently. The patient was seen 13 months after the onset at which time she felt well and was gaining weight, although small ecchymoses still appeared on the skin. The clotting time was 76 minutes.

It was thought by Dreskin and Rosenthal (273) that the patient had either a deficiency of thromboplastin or the thromboplastin precursor in her plasma which was probably secondary to the excess of anticoagulant substance, the anticoagulant either neutralizing or destroying the thromboplastin precursor.

The authors propose (273) that the term hemophiloid disease be used to designate a definite syndrome characterized by hemorrhagic manifestations, prolonged coagulation time, and a circulating anticoagulant possibly arising as a result of immunization against a globulin factor.

Fibrinogen and Fibrin.—Fibrinogen, a blood protein, is present in the plasma to the extent of about 0.3 gram per 100 cc. of plasma. It may be defined as the plasma protein which is converted to fibrin by thrombin. The molecular weight of the substance has been estimated to be 63,000 by Bergmann and Niemann (274) but more recently Nanninga has stated that it is 441,000 (275). Fibrinogen is a protein resembling the globulins but differing in a few precipitation reactions. It is converted to fibrin, an insoluble compound which serves as the basis for the blood clot.

The end result of blood coagulation is the formation of fibrin taking the shape of a network of fibers that enmesh the formed elements of the blood. The freshly formed fibers possess the quality of extreme adhesiveness which causes them to adhere to each other, the blood cells, the tissues, and foreign surfaces. Once developed the fibers have the specific capacity to contract, squeezing out serum with a small proportion of red blood cells, thereby reducing the size of the original clot about

with this condition *repeated hemorrhages from the nose* had reduced the hemoglobin to 55 per cent with the usual incapacitation which is associated with that degree of anemia

Diagnosis.—The presence of a bleeding *tendency especially* with hemorrhages from the nose the gums and following slight trauma to the skin with a prolonged bleeding time and a normal coagulation time retractility to the clot, and platelet count and a negative tourniquet test point positively to the diagnosis. Such a condition is not true hemophilia because the coagulation time is normal and females as well as males may be affected and both may transmit the disease. Thrombopenic purpura can be excluded because the blood platelets are not decreased and usually the clot retracts normally.

With a history of repeated epistaxis one should be sure to determine that the excessive bleeding from the nose is not due to the vascular lesions of hereditary hemorrhagic telangiectasia. This condition should be readily differentiated because the presence of the multiple dilatations *of small vessels in the skin and mucous membranes* characteristic of the disease are usually apparent.

Treatment and Prognosis.—The prognosis according to Bailey and McAlpin *(269)* is *good as the condition tends to have its onset* in childhood and become less active as the child grows older. On the other hand the extensive and prolonged hemorrhages may incapacitate a patient for long periods of time and cause death in some instances.

Various local measures to control the bleeding are usually without avail. Of all forms of treatment employed blood transfusions are the most satisfactory, although their effects are transient. They do not affect the prolonged bleeding time. Splenectomy is contraindicated.

Hemophilia Like Disease Due to Circulating Anticoagulants.—In 1940 Lozner Joliffe and Taylor *(270)* reported the first case of a patient with hemorrhagic manifestation due to a circulating anticoagulant. Circulating anticoagulants have been found in patients with obvious hemophilia and also in association with various diseases or as a primary form which *manifests itself by symptoms identical with those of hemophilia*. The first type of case is thought to develop the anticoagulant as a result of immunization following blood transfusions. Antibody formation may be *stimulated by the antihemophilic globulin which is absent from* the blood of patients with hemophilia but supplied by the transfused blood (272) or by injection of the purified antihemophilic globulin. In the second *type of case* apparently the anticoagulants are of a different nature *(271)* as the antibodies may arise *de novo*. It is suggested that the term "hemophilia like disease" be reserved for this condition.

The characteristics which distinguish this disorder from true hemophilia are that the onset may be late in life and the condition occurs in females as well as males. It may be recognized by adding a small

no deficiency of fibrinogen or any other component of the blood but there is a prolonged tendency to bleed although the coagulation time is normal In fibrinogenopenia there is no primary abnormality present in the blood other than the bleeding tendency due to the absence or diminution in the amount of fibrinogen Loss of a sufficient amount of blood may of course cause a hypochromic microcytic anemia It seems to be characteristic for patients thus afflicted to have long periods of remissions despite the fact that the fibrinogen is still absent from the blood The bleeding appears to resemble that observed in hemophilia but joint involvement is not common

The diagnosis according to Quick (286) is simple as he states that it is the only hemorrhagic disease in addition to acute yellow atrophy in which the blood remains absolutely and permanently incoagulable It is possible to establish the fact that fibrinogen is absent from the plasma by saturating it with sodium chloride or quarter saturating it with ammonium sulfate As these two methods will precipitate the fibrinogen the failure of a precipitate to appear indicates the complete absence of this normal component of the blood Furthermore as fibrinogen is coagulated by heating to 70 degree C the persistence of a clear fluid plasma following the heating to this degree indicates the absence of fibrinogen

Patients with this condition are always in danger of death from hemorrhage although they may continue to live in good health for some years Death usually occurs however in childhood

Acquired Fibrinogenopenia —This condition is rare because the normal concentration of fibrinogen which is 0 2 to 0 4 per cent must be reduced to below 0 02 per cent before an abnormal bleeding condition develops Further studies by accurate methods of estimating fibrinogen are necessary before definite conclusions can be drawn concerning the prevalence of this condition According to Risak (282) a reduction in the amount of fibrinogen has been observed in myelogenous leukemia and various types of malignancy as well as in certain infections such as brucelliasis pneumonia and tuberculosis It has been stated (286) that the bleeding in acute yellow atrophy of the liver which had been attributed to a low fibrinogen is very likely due to a pronounced hypothrombinemia

Treatment —The only known treatment of the condition is the administration of blood or plasma transfusions which will supply a certain amount of fibrinogen and thereby have a tendency to check the bleeding

The Role of Calcium in the Clotting Process —The calcium of the blood is found almost entirely in the plasma in amounts varying normally between 9 0 and 11 5 milligrams per 100 cc About 60 per cent is diffusible and probably almost all of it is in the ionic form The remainder is in the non diffusible form and is probably attached to the serum albumin As long ago as 1890 Arthus and Pages (287) demon

40 per cent (276) This contraction is attributed to some extent to the blood platelets, for it is incomplete or almost wholly absent when there is a thrombocytopenia There is evidence that the platelets attach themselves to the fibrin threads and, in some manner cause these fibers to bend and twist thereby producing a contraction of the clot which is an essential step in hemostasis

The general assumption has been that fibrinogen is formed in the liver Evidence in favor of this was discovered by Nolf (277) who demonstrated that by excluding the liver from the circulation the fibrinogen content of the circulating blood fell rapidly This belief was substantiated by observations following hepatectomy (278) and after producing liver damage by poisoning with chloroform and phosphorus (279) Evidence is available however which indicates that injury to the liver may not only result in a diminished production of fibrinogen but there may also be an increased destruction of the material due to operative procedures and after poisoning with chloroform and phosphorus (280) The decrease of the circulating fibrinogen therefore in experimental animals may be on the basis of two mechanisms

The Relationship of Diminished Fibrinogen of the Blood (Fibrinogenopenia) to Abnormal Bleeding—Both congenital and acquired fibrinogenopenia are exceedingly rare conditions which are of interest largely from a theoretical standpoint A few cases of the congenital variety of the disease have been reported in children and infants in which there has been subcutaneous bleeding and uncontrollable hemorrhage following minor injuries The absence of fibrinogen has been established in some instances by the failure to obtain a precipitate when either the serum is heated to 65 degrees C or when 25 per cent saturation with magnesium sulfate is produced On the addition of fibrinogen to the serum a normal clot may be obtained (281) In some cases the fibrinogen may not be entirely absent but be greatly reduced Such a state has been designated by Risak (282) as a constitutional fibrinopenia and by Schonholzer (283) as a constitutional hereditary fibrinogenopenia The literature on this subject has been reviewed by Henderson Donaldson and Scarborough (284)

By some (283 285) it is considered that the condition is inherited on the basis of a recessive mendelian characteristic which is not sex linked Convincing proof is not available in support of this view at present Studies of the familial incidence of the condition have been hampered because of the scarcity of satisfactory determinations of fibrinogen in a large number of persons

Symptoms—This condition has been designated as a pseudohemophilia by some The term has been so employed especially in the German literature but it should be reserved for the bleeding disorder originally described by von Willebrand (261) In the latter condition there is

blood platelets and causes an alteration in the osmotic pressure which results in rupture due to the imbibing of water. In this way it is thought that the thromboplastin is released. Evidence has been presented by Stefanini (290), however, that sodium oxalate acts as an anticoagulant not only by precipitating calcium but also by removing the element from combination with a factor which is essential for normal clotting. Furthermore, it is his belief that sodium citrate prevents clotting by combining with one or more factors of the prothrombin complex. He concludes with the statement that the evidence which he has given in the article indicates that the combined and not the ionized calcium is the factor which is active in the coagulation of the blood.

Although the blood calcium may be greatly reduced in certain disease states such as tetany, there is no change in the process of blood clotting. According to Crane and Sanford (295) it is only when the blood calcium is reduced to 2.5 milligrams per cent or less that there is a pronounced prolongation of the coagulation time. In the present stage of our knowledge it can be said that prolongation of the clotting process giving rise to abnormal bleeding is not known to be due to any alteration in the amount of circulating blood calcium.

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strated that the removal of calcium prevented the coagulation of blood and restored clotting. Since that time it has been the general belief that calcium plays an indispensable role in the clotting process which cannot occur in the absence of the ionized element. It has been shown by Seegers however (288) that when purified prothrombin is placed in a 30 per cent sodium citrate solution it will slowly be converted to thrombin thereby demonstrating that it contains all the structural material required for the formation of thrombin and that calcium thromboplastin and plasma accelerator globulin function only as activators of prothrombin in this stage of coagulation

A comprehensive review of the role of calcium in the coagulation of the blood was written by Ferguson (289) in 1936 and more recently one by Stefanini (290) has appeared. The latter author finds that the optimum concentration level for the coagulation of whole blood or plasma is 1.5 millimols (0.006 per cent or 6 milligrams per 100 cc) which is below the concentration in the circulating blood. The optimum concentration for the conversion of prothrombin to thrombin is 2.5 to 10 millimols (0.01 to 0.04 per cent or 10 to 40 milligrams per 100 cc). Although strontium and to a lesser extent magnesium can act as clotting agents they are not as effective as calcium

According to Stefanini (290) all phases of the clotting process are affected by calcium at least in artificial experimental conditions as follows the activation of thromboplastin the conversion of prothrombin to thrombin and the action of thrombin on fibrinogen. It is reported by Laki and Lorand (291) that calcium affects the fibrinogen fibrin transition and evidence has been found that it also influences the rigidity of the blood clot. Recently it has been noted by Rosenfeld and Janszky (292) that calcium plays an important accelerating role in the clotting of fibrinogen either when acting alone or as a component of an unidentified factor. Thus it is apparent that calcium functions in more than one phase of the clotting process and undoubtedly there still remains much which is unknown about this element and its relation to blood coagulation

It is the knowledge of the essentialness of calcium to the clotting process that led to the use of the soluble salts of citrates oxalates and fluorides as anticoagulants. For by their action the calcium is in some manner prevented from participating in the clotting mechanism. The mechanism by which this occurs is not known but Quick (293) offers the suggestion that calcium is combined with the prothrombin molecule itself and on the addition of the decalcifying agent this calcium is released from the prothrombin leaving the latter in an inactive state that cannot be converted to prothrombin regardless of how much thromboplastin is available. Another theory (294) is that the calcium in some unknown manner acts upon the platelets and causes them to release the thromboplastin. According to Ferguson (294) the calcium enters the

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CHAPTER XIV

HEMORRHAGIC STATES

Platelet Deficiencies

Definition.—A hemorrhagic state may be defined as an abnormal tendency to bleed into the skin, mucous membranes, the viscera, and other tissues. It is usually due to some defect in the clotting process or an increase in the permeability of the blood capillary walls.

History.—The conspicuousness of purpuric spots on the skin makes this disorder so noticeable that early descriptions of the conditions are to be expected. The word purpura, according to Jones and Tocantins (*1*), is the Latin derivative from the Greek word *porphyra*, meaning purple fish (purpura lapillus), a gastropod mollusk, from the gills of which is obtained a purple dye. Although it was used by the Greeks and Romans as a designation for changes in the skin and mucous membranes to which the term purple could be applied, it did not come into general use in medicine until the sixteenth century. At this time it was employed to indicate the purpuric rash observed in the plague, cerebrospinal fever, and typhus fever.

The history of the development of our knowledge concerning purpura has been divided into three arbitrarily designated periods by Jones and Tocantins (*1*). The first phase dates from the very earliest times when purpura was invariably described in association with the pestilential fevers. This period ended in 1556 with the descriptions of Lusitanus (*2*) and of Riverius (*3*) in which purpura was recognized as a separate disease entity. During this second interval attempts were made to separate purpura into various types, such as Schonlein's and Henoch's purpura, but very little was known concerning the underlying mechanism responsible for the production of the syndrome. The third phase was inaugurated by the highly important discovery that the number of blood platelets is greatly reduced in some forms of purpura. This was first noted by Krauss in 1883 (*4*) and Denys in 1887 (*5*). This was the beginning of the third or modern phase in which the contributions of Hayem, Duke, Kaznelson, and others gave us the present day conception of the disease.

In 1557 Amatus Lusitanus (*2*) described the case of a young girl whose body was apparently covered with purpuric spots and bloody discharges were present. There was no fever and the patient eventually recovered. This is one of the first cases of purpura reported which was

not associated with epidemic fever of one sort or another In 1658 Eugalenus (*6*) described several cases in which hemorrhages into the skin were accompanied by bleeding from the mouth and gums

The reference to purpura by Paul Gottlieb Werlhof (*7*) from which the designation Werlhof's disease is derived consists of a single brief case report The patient described was an adolescent girl who had epistaxis vomiting of blood and apparently purpuric areas on her neck and arms These were described as spots partly black partly violescent or purple such as often seen in malignant small pox the number of spots increasing and surrounding completely both of the eyes the back of the nose and the skin around the mouth and chin with a livid black color like marked from bruises After seeing the name Werlhof's disease referred to so many times one is disappointed in this brief, rather fragmentary note with reference to only one case which has served for so many years as the basis for the use of Werlhof's name to indicate the disease

The Blood Platelets in Purpura—The blood platelets were first recognized by Alexander Donne in 1842 (*8*) who called them globulins Several years later they were described independently by Zimmermann (*9 10*) who used the term Elementarkoperchen or elementary corpuscle A classical description was also given by Schultze (*11*) in the first volume of the Journal founded by him Osler's description appeared in the *Proceedings of the Royal Society* for 1874 (*12*) and also in *Medical News* (*13*) Apparently the article by Bizzozero (*14*) dealing with the platelets surpassed all others for accurate detail up to this time and placed them on a firm hematological basis It was he who introduced the term blood platelet and recognized their importance in blood coagulation and thrombus formation

The article by Osler (*12*) published in 1874 infers from the title that the platelets are certain organisms In the substance of the publication however this inference is corrected to a certain extent by the statement that nothing can be said of their relation to bacteria He refers to the previous work of Max Schultze (*11*) and that of Riess (*15*) but neglects to mention the original description of the platelets by Alexander Donne in 1842 The paper is concluded with the statement that we know nothing of the origin or destiny of these corpuscles Riess assertion that the masses arise from the disintegration of white corpuscles becomes quite untenable We must also confess the same ignorance of their increase in disease nor do we know at all what influence they may exert in the course of chronic affections Finally Osler states "as there is no evidence that these bodies are in organic continuity with any other recognized animal or vegetable form or possess the power of reproduction nothing can at present be said of their nature or of their relation to bacteria The source of the blood platelets was obscure until 1906 when James Homer Wright (*16*) described their origin from megakaryocytes

Observations on the Reduction of the Number of Platelets—The highly significant observation that the blood platelets are reduced in some cases of purpura was first made by Krauss (4) and later by Denys (5) Professor of Pathological Anatomy at the University of Louvain in Belgium The latter reported the case of a patient in whom the coagulation process was retarded and there was a considerable reduction in the number of platelets of the circulating blood It was not until 1895 however that Hayem (17) actually counted the number of platelets in a patient with purpura He found in one case that they were reduced to 89 000 per cubic millimeter In this same article it was noted for the first time that the clot would not retract and express serum Hayem termed the platelets "hematoblasts"

Clot Retraction—The earliest observations on the abnormal character of the clot in purpura hemorrhagica was by Johnston in 1822 (18) He observed a fatal case of purpura and performed a necropsy on the patient Among other findings he reported that "the blood drawn in the morning has not separated into serum and crassamentum (note after an interval of several hours) It possesses little consistence or tenacity but there are traces of coagulable lymph diffused through it" In the same Journal and immediately following the article by Johnston is a short paper by Andrew Duncan (19) in which he describes a similar case and refers to the failure of the clot to retract as follows " the blood was observed to have an unusual appearance It coagulated very slowly nor was the coagulum very firm No serum was separated The coagulum had the appearance of jelly being with a pink tinge from the red globules which had sunk to the bottom seen through it" As previously mentioned however it was Hayem who not only later made this same observation but added the highly significant information that this phenomenon was associated with the diminution in the number of platelets

Bleeding Time—The studies of Duke in 1910 (20) served to differentiate the bleeding time from the coagulation time and hence to emphasize the difference between the hemorrhagic tendency in hemophilia and in purpura Duke made the point that in patients with a hemorrhagic tendency due to a diminution in the number of platelets and associated with a non retractility of the blood clot the diagnosis may be corroborated and the progression of the disease noted by determining the bleeding time according to the method which he devised It had been recognized previously however that the bleeding time was prolonged in certain cases of purpura For example Stoker in 1823 (21) determined the coagulation time in one of his cases of purpura was nine to 19 minutes and the "flowing time" from three to seven minutes It had also been observed by Henoch in 1882 that prolonged bleeding might follow pricking the skin in these patients

Capillary Resistance Test—As early as 1810 it was observed by Sir John Pringle (22) that petechiae appeared below the tourniquet when

it had been applied for venesection in certain patients with hospital fever" This test was introduced into France in 1911 by Weill and Chalier (23) In Germany it is designated as the Rumpel Leede phenomenon (24) In the United States it was first used by Hess in 1914 (25) and is known as the capillary resistance test According to Jones and Tocantins (1) undoubtedly the first to describe this diagnostic procedure however, was Frugoni and Giugni in Italy in 1911 (26)

The Use of Blood Transfusions in the Treatment of Purpura —The earliest case in which the patient was treated for purpura by the transfusion of blood is credited to Warrington Haward (27) who injected 11 ounces of blood into a child who was moribund from purpura hemorrhagica in 1873 The patient succumbed several hours after the transfusion In the same year Thomas Smith (28) transfused a young girl of eight years who had a purpurous eruption on various parts of her body, with such extensive bleeding from the nose as to cause her to be absolutely blanched Eleven ounces of blood were drawn from a healthy donor defibrinated with an egg beater and injected into the patient's veins This therapeutic measure is of great historic interest but failed to help the patient as she succumbed two and one half hours after the transfusion had been given In the following year T G Morton of Philadelphia (29) gave two ounces of defibrinated blood to a patient with purpura with immediate improvement and eventual recovery

In 1910 W W Duke (20) advocated the use of blood transfusions in the treatment of purpura with active bleeding He emphasized that transfusion gives good results in the treatment of the disease because in addition to replacing blood it stops hemorrhage for a few days and may tide the patient over a serious crisis He suggested that such treatment is probably applicable to the symptomatic as well as the idiopathic types of the disease Duke insisted that transfusion must be done by the direct method as defibrinated blood is free from platelets and is therefore of no value in increasing the platelet count It should be recalled that the citrate method of blood transfusion was not introduced by Hustin until May 1914 and was not used extensively in this country until the following year

The Introduction of Splenectomy as a Form of Treatment in Purpura — In 1915 Frank (30) proposed the theory that a diminished production of the blood platelets resulted from the toxic action of the spleen which inhibited their formation from the megakaryocytes in the bone marrow On the other hand Kaznelson (31) had frequently noticed enlargement of the spleen and came to the conclusion that an increased function of this organ in destroying platelets was responsible for their diminished number in the blood stream According to Brill and Rosenthal (32) and Jones and Tocantins (1) it was Kaznelson who first had a splenectomy performed in patients with this condition In 1938 however it

is stated by Rosenthal (33) that from the theoretical considerations of Frank (1915) splenectomy in the treatment of thrombocytopenic purpura appeared to have possible therapeutic value The first two cases splenectomized at the suggestion of Hess (1915) were fatal The first successful case was reported by Kaznelson (1916)

In 1917 Hess (34) concluded from his experiments that the deficiency of circulating platelets in purpura is due to a destruction of these cells Furthermore on account of the claim that in purpura there is frequently a hemolytic substance in the plasma which renders it exceedingly difficult to find compatible donors for transfusions and because the removal of the spleen in man and animals brings about a definite increase in the number of blood platelets it would seem worthy of trial to perform a splenectomy in severe cases of purpura where extreme therapeutic measures had been resorted to in vain In the opinion of Jones and Tocantins this suggestion was an entirely independent one without the knowledge of the observation of Kaznelson (31)

Classification —The classification of the hemorrhagic states is difficult because there are so many diverse causes which may be responsible for these conditions and also because an etiologic classification which is the form given below must necessarily be based upon incomplete and sometimes controversial information Any arrangement into the various groups must at present be regarded as tentative in nature and subject to revision when new and helpful knowledge is added to this field In the meantime it is of assistance to attempt a systematic grouping of this rather large number of conditions

In general it is not difficult to state that all hemorrhagic disorders can be divided into three large groups as follows 1 those apparently due solely to a decrease in blood platelets 2 those resulting from increased capillary permeability and 3 those associated with other deficiencies in the elements of the blood which are necessary for the normal clotting process There is undoubtedly some overlapping of these categories but in general most of the abnormal bleeding conditions can be placed in one of these three divisions without too much difference of opinion

The first group the thrombopenic purpuras which are characterized by a striking reduction in the platelets of the circulating blood can be subdivided further into the idiopathic type in which the cause cannot be recognized and the secondary varieties in which the thrombopenia is due to some associated condition such as a hematopoietic disorder infection or cancer It has been necessary within recent years to add an additional division which was not present in the older classification This is the one which has been designated as allergic thrombopenia It was created to include those hemorrhagic disorders which are due to various allergins such as drugs and certain articles of diet There is no question but what these substances can cause a decrease in platelets associated

with abnormal bleeding but it is somewhat of an assumption when one considers that the mechanism of this is truly an allergic one This explanation seems to be the most logical one however which has been offered up to the present time Furthermore, in some cases it is possible that the purpuric manifestations may be due to increased capillary permeability which is also on a possible allergic basis as well as the thrombopenia Hence in some patients the bleeding attributed to this phenomenon may be regarded as having a dual explanation

The second large division which is made up of abnormal bleeding states attributed to changes in the capillary walls is the most important of all from the standpoint of frequency for it is by far the one most commonly encountered This group includes the purpura seen in many different types of infections in nephritis and in scurvy In this section are also included the rather rare purpuras of Schonlein and Henoch which appear to be more important from the standpoint of historical interest and the prominence given them by the early publications of Osler rather than their frequency They have been assigned to this section because it is likely that these purpuric manifestations are on the basis of some defect of the capillary wall which is probably an allergic manifestation Furthermore it becomes necessary to include in this group the nonthrombopenic purpuras apparently due to food and drug sensitivity although additional studies which have a bearing on this group are desirable It is made up largely of many single case reports in which purpuric signs have appeared following the administration of certain drugs or the ingestion of various articles of diet The sequence of events which all agree may be very misleading cannot always be accepted as scientific proof of a causal relationship Nevertheless the field of allergy is a very promising one in relation to the purpuric states and no doubt information of this nature which will be made available in the future will do a great deal to clarify this type of hemorrhagic disorder

The third main division has to do with the changes which may occur in the normal components of the blood, other than the platelets which are responsible for the clotting process As long as there remains a difference of opinion concerning the nature of the normal process of blood coagulation it is not possible to adopt anything but a tentative grouping in this division Nevertheless the one suggested which is based on one of the modern theories of blood clotting and the recent developments in the relationship to vitamin K to prothrombin formation is helpful from the standpoint of clinical classifications of these disorders

CLASSIFICATION OF THE HEMORRHAGIC STATES

I Hemorrhagic States Due to a Decrease in the Number of Blood Platelets (Thrombopenic Purpura)

A *Idiopathic Thrombopenic Purpura (Purpura Hemorrhagica)*

B Symptomatic Thrombopenic Purpura

1 In association with blood diseases
   (a) Leukemia
   (b) Aplastic anemia
   (c) Pernicious anemia
   (d) Sickle cell anemia
   (e) Hemolytic anemia
   (f) Banti s disease
   (g) Gaucher s syndrome
   (h) Felty s syndrome

2 Infections
   (a) Typhoid fever
   (b) Meningococcus infections
   (c) Upper respiratory infections
   (d) Septicemia
   (e) Typhus fever
   (f) Miliary tuberculosis
   (g) Smallpox
   (h) Vaccinia
   (i) Lupus erythematosus
   (j) Subacute bacterial endocarditis
   (k) Infectious mononucleosis

3 Cancer (bone marrow metastases)
   (a) Cancer of the stomach
   (b) Multiple myeloma
   (c) Any malignant neoplasm which may metastasize to the bone marrow

4 In cirrhosis of the liver

5 Allergic thrombopenia
   (a) Drug allergy
      (1) Organic arsenicals (arsphenamine etc)
      (2) Sedormid
      (3) Gold preparations
      (4) Benzol
      (5) Sulfonamide drugs
      (6) Quinine
      (7) Possibly ergot bismuth phenobarbital bismuth iodides and others
   (b) Food allergy

II HEMORRHAGIC STATES DUE TO CHANGES IN THE CAPILLARY WALLS (NON THROMBOPENIC PURPURA)

A Infectious Diseases

1 Endocarditis
2 Typhus fever

3 Meningitis
4 Septicemia
5 Pneumonia
6 Typhoid fever
7 Tuberculosis
8 Chronic infections such as pyelonephrosis lung abscess etc
9 Scarlet fever
10 Waterhouse Friderichsen syndrome

B Toxins of Nephritic Origin

C Schonlein Henochs Purpura (Anaphylactoid)

D Drug and Food Sensitivity

E Vitamin Deficiency

1 Vitamin C deficiency (scurvy)
2 Vitamin P deficiency

F Abnormal Capillary Fragility in the Newborn

G Hereditary Familial Purpura Simplex

III HEMORRHAGIC STATES DUE TO CHANGES IN THE NORMAL CLOTTING ELEMENTS OF THE BLOOD

A Deficiency of Prothrombin

1 Due to dietary defects of vitamin K
  (a) Hemorrhagic disease of the newborn
  (b) Dietary defects in adults
2 Faulty absorption of vitamin K
  (a) Jaundice and bile fistula
  (b) Sprue
  (c) Chronic ulcerative colitis and other chronic intestinal conditions
3 Impaired formation of prothrombin by the liver
  (a) Cirrhosis of the liver
  (b) Banti s disease
  (c) Felty s syndrome
  (d) Acute yellow atrophy
  (e) Chloroform carbon tetrachloride and phosphorus poisoning
4 Inactivation of prothrombin (dicoumarin)
5 Idiopathic prothrombinemia

B Abnormal Bleeding Due to Qualitative Changes in the Platelets

1 Hemophilia due to a decreased amount of thromboplastin
2 Chronic hereditary thrombobasthenia

C Fibrinogen Deficiency

1 Acquired fibrinogenopenia (nutritional disturbances phosphorus poisoning severe liver damage)
2 Congenital fibrinogenopenia (pseudohemophilia)

D Circulating Anticoagulants

1 Liberation of heparin in the blood
   (a) Peptone shock
   (b) Anaphylactic shock

2 Excessive antithrombin

A classification of the hemorrhagic disorders by Doan (35) which has been slightly modified is as follows

CLINICAL PURPURIC SYNDROMES

1 Non thrombocytopenic
   a Plasma deficit (prothrombin fibrinogen etc)
   b Capillary defect (increased permeability)

2 Thrombocytopenic
   a Hypersplenism
      1 Primary (idiopathic thrombocytopenic purpura)
      2 Secondary (Hodgkin s disease Boeck s sarcoid etc)
   b Megakaryocytic inadequacy
      1 Aplasia (aplastic anemia)
      2 Displacement (leukemia lymphosarcoma)
      3 Toxic destruction (chemicals infections physical)
      4 Deficient nutritional factors (vitamin deficiencies etc)

The classification of the purpuras as given by Wintrobe (36) is as follows

I THROMBOCYTOPENIC PURPURA

A Essential or Primary Purpura Hemorrhagica (Werlhof s Disease)

B Symptomatic

1 Chemical vegetable animal and physical agents
   a Chemical—organic arsenicals sedormid gold salts benzol possibly phenobarbital dinitrophenol quinine ergot bismuth iodine organic hair dyes sulfonamides streptomycin tridione
   b Vegetable—foods orris root
   c Animal—snake venoms pertussis vaccine extensive burns
   d Physical—x rays and other forms of ionizing radiation heat stroke

2 Blood disorders
   a Leukemias acute or late stages of chronic
   b Anemias aplastic idiopathic or due to chemical or physical agents myelophthisic (tumors in bone marrow osteosclerosis etc) pernicious anemia
   c Splenic disorders Banti s and Gaucher s disease

Felty s syndrome, hemolytic icterus rarely Hodgkins disease

d Miscellaneous Acute purpura with platelet thrombi in capillaries purpura hemorrhagica with lymphocytosis

3 Infections and other conditions septicemia subacute bacterial endocarditis typhus lupus erythematosus disseminata sarcoidosis etc

II NON THROMBOCYTOPENIC PURPURA

A *Allergic Purpura Purpuras of Henoch and Schonlein Erythemas of Osler*

B *Symptomatic*

1 Infections subacute bacterial endocarditis, meningococcal sepsis typhoid influenza, scarlet fever smallpox measles diphtheria

2 Chronic disease chronic nephritis cardiac or hepatic disease, hemochromatosis

3 Chemical and animal agents iodides copaiba belladonna atropine quinine bismuth mercury phenacetin salicylic acid chloral hydrate merbaphen, snake venoms

4 Avitaminosis scurvy

5 Certain skin diseases Ehlers Danlos syndrome Majocchis disease Schamberg s disease etc

C *Hereditary Hemorrhagic Diathesis (Thrombasthenia)*

D *Miscellaneous Forms of Purpura Purpura Simplex Fulminans Senilis Cachectica Mechanical Orthostatic David s Disease*

Incidence of Different Types of Hemorrhagic Disorders—The most frequently encountered type of hemorrhagic state is that associated with the infectious diseases and this in a great majority of instances is a purpuric condition due to local capillary injury with resultant increased permeability It should be emphasized however that the hemorrhagic aspect of an infectious disease is often a minor one which may play only an insignificant role in the production of the patient s symptoms and be of little importance in formulating the prognosis On the other hand experience has shown that the hemorrhagic varieties of certain infectious diseases such as black smallpox have an ominous prognosis Various blood dyscrasias are commonly associated with an abnormal tendency to bleed but the hemorrhagic state is often secondary to widespread hematopoietic changes which are usually of far greater importance The bleeding state therefore should be regarded as only an incident and often a terminal one in a blood disorder of long standing This is true for example of the bleeding tendency which is commonly observed in chronic nephritis It is characteristic of the terminal state when the patient is either in uraemia or bordering on it

From the standpoint of incidence the bleeding condition associated with jaundice is of importance not only because it is relatively common but because the investigations of recent years have shown that it is due to vitamin K deficiency and a decrease in the prothrombin of the circulating blood which can be corrected by means of vitamin K therapy

The incidence of idiopathic thrombopenic purpura is not great as it probably makes up only about 2 to 3 per cent of all cases of abnormal bleeding It is of importance however because in many of these cases relief may follow splenectomy

As an indication of the incidence of the various factors responsible for the hemorrhagic states the following table is given from the observations of Perlman and Fox (37) It should be emphasized however that this information concerning the incidence of the various hemorrhagic states is based on data obtained at necropsy It is evidence of the frequency therefore of hemorrhagic states as they occur in fatal disorders only This would mean that various other hemorrhagic conditions which are mild in nature are not included The incidence of factors responsible for hemorrhagic states then from necropsy statistics as given by the above authors is as follows

1 Infectious diseases	49 3 per cent
2 Platelet deficiencies	21 9 per cent
3 Pathologic renal conditions	16 3 per cent
4 Hepatic disorders	9 19 per cent

IDIOPATHIC THROMBOPENIC PURPURA

Synonyms —Purpura Hemorrhagica Essential Thrombocytopenic Purpura Werlhof's disease

Definition —A disease of unknown etiology most commonly occurring in children and young adults characterized by spontaneous bleeding in the skin from the mucous membranes and into various tissues by a striking decrease in the blood platelets of the circulating blood a prolongation of the bleeding time a normal coagulation time and a positive tourniquet test Usually the only changes in the blood are the thrombocytopenia and those secondary to blood loss

Etiology —**Incidence** —It is recognized that the disease occurs most frequently in children and young adults and in the female sex In our cases about one half occurred in the first two decades In the male the greatest incidence was in the first decade in the female there was about an equal incidence in the second and third decades In the 62 cases reported by Wintrobe and his associates (38) the disorder appeared before the age of 12 in 40 cases (64.5 per cent) and in 15 more symptoms developed between the ages of 12 and 24 years making a total of 88 7 per cent in the first 24 years of life These same authors

reported the age incidence according to decades in 271 collected cases as follows first decade 36 9 per cent of the cases second decade 27 4 per cent, third decade 17 1 per cent fourth decade 8 7 per cent fifth decade 6 1 per cent sixth decade 3 8 per cent

In general it may be said that about 80 per cent of the females and 70 per cent of the males have an onset of the disease before the age of 40 years It should be noted that patients do have the onset of this disease after 40 years but it should be kept in mind also that other diseases causing purpura are more common at that age

From these figures it is apparent that only a comparatively small per cent of the cases have their onset after the age of 40 years Any patient past that age who develops suggestive evidence of thrombopenic purpura *should be investigated most carefully to exclude such possible causes as* leukemia or malignancy which would place it in the secondary thrombopenic class

Sex —The disease predominates in the female sex usually in a ratio *which is given as 2 1 but some believe that the proportion is nearer 4 3 (38)* In our own group of 91 cases the incidence was twice as great in the female This increased incidence in the female sex and the claim that relapses occur more commonly following splenectomy in females than males suggest the possibility that some endocrine disturbance may play a role in its etiology It is of interest to note that of the women the initial symptom is menorrhagia in about one in every five cases

Race —According to some observers (*38*), the disorder is less prevalent in Negroes than in white persons For example it was found to be present in only four Negroes in a series of 62 patients observed at the Johns Hopkins and Union Memorial Hospitals in Baltimore whereas the ratio of the Negro to white persons admitted in these institutions was 3 7

Heredity —There is suggestive evidence that heredity plays a role in this type of purpura although the evidence in support of this is not as clear as in the recognized familial or hereditary form of purpura in which the platelet count is normal It was very unusual to find a family history of purpura or abnormal bleeding in our group of cases Both Hess (*39*) and Witts (*40*) have reported instances however in which more than one case has appeared in the same family It is not uncommon to find that other blood relatives are said to bruise easily, but this can only be accepted as suggestive rather than conclusive evidence of an hereditary trend Whitney and Barritt (*41*) have reviewed the literature dealing with this phase of the disease and have found 14 cases of congenital thrombopenic purpura to which they add two new cases They report that the first child born to a mother who had undergone splenectomy for the disease 12 years prior to the pregnancy was covered with purpuric spots and died on the third day of life The platelet count was

80 000 per cubic millimeter A second child was born some time later and this infant likewise showed petechiae at birth and had a platelet count of 90 000 per cubic millimeter It is now generally accorded that a mother with idiopathic thrombocytopenic purpura is likely to give birth to a child with the same disorder which usually persists for only a brief interval The disorder *is transmitted probably because there is a hormone like substance in the blood of the mother which crosses the placenta and acts on the blood of the fetus This is discussed more fully* under the heading of Purpura in Pregnancy on page 650

Mechanism of the Cause of the Disease—There is unanimous agreement by all students of the disease that the immediate cause of the bleeding is related in some manner to the reduction in the number of circulating platelets This may be due to inadequate clot formation and the failure to plug openings in the small vessels the inability of the clot to retract properly or to some disturbance of the obscure relationship between the platelets and the permeability of the capillaries

Although there is general agreement with the view that the blood platelets are vitally concerned with the clotting of the blood and that bleeding is likely to occur when they are deficient in numbers the problem of pathologic hemorrhage in this condition is not so easily explained In general when the blood platelets decrease below 100 000 per cubic millimeter there is a tendency to spontaneous hemorrhage and when the count is below 50 000 this is usually marked On the other hand there are exceptions to this statement which have caused a great deal of discussion concerning the possibility that some other factor such as changes in the capillaries may play a role in the production of the bleeding It is known for example that the spleen may be removed with control of the hemorrhagic tendency and yet the number of blood platelets remains below normal Also some patients may have purpuric *manifestations with a fairly high platelet count and others do not*

Some of the main problems relating to the etiology of the disease about which more information is necessary before a definitive answer can be given are as follows 1 is the diminution in platelets due to their increased or decreased destruction 2 what is the fundamental cause of the thrombopenia 3 what other factors in addition to the thrombopenia are responsible for the abnormal tendency to bleed, 4 what role does the spleen play in relation to the number of platelets in the circulating blood and 5 what is the mechanism whereby splenectomy and ACTH and Cortisone exert their beneficial action

There are three main views concerning the possible cause of the thrombocytopenia in this condition They are first that the *platelets* undergo hypersequestration in the spleen and are destroyed there—a theory that was *originally suggested by Kaznelson (42)* in 1916 and supported by Wiseman Doan and Wilson (43) Second that the spleen

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blood Instead of the term "hypersplenism" as applied to this form of purpura they would employ the designation of "immunothrombocytopenia" Their theory is based on the observation made by Bedson and Johnson (49) which showed that the injection of an antithrombocyte serum into animals produced a thrombocytopenia purpura and a proliferation of megakaryocytes in the bone marrow These experiments indicated that this form of purpura might be due to some immune mechanism similar to that observed in acquired hemolytic anemia Furthermore suggestive but not conclusive evidence has been produced by Evans and his associates (46) that there is a thrombocyte-agglutinating factor in the blood of patients with idiopathic thrombocytopenic purpura They liken the latter disease to acquired hemolytic anemia which is now considered to be due to the action of an autoantibody and cite instances well substantiated that the two hematological disorders may occur simultaneously in the same person

The theory of Evans and his collaborators is strengthened by the observations of Harrington and his associates (50) who have recently demonstrated beyond the slightest question of a doubt that at least in some patients with idiopathic thrombocytopenic purpura and secondary thrombocytopenic purpura there is a thrombocytopenic factor in the whole blood and plasma They observed that the intravenous administration of 500 cc of whole blood or its plasma equivalent taken from patients with these forms of purpura caused a prompt and often dramatic decrease in the blood platelet counts of non thrombocytopenic recipients This decrease persisted for from five to seven days When the thrombocytopenia was severe it was associated with a prolonged bleeding time and a decreased prothrombin consumption There is suggestive evidence that the thrombocytopenic factor is present in the globulin fraction of the plasma It is of interest to note that the platelet reducing factor was demonstrated in two patients with idiopathic thrombocytopenic purpura prior to splenectomy and that it remained even after a return of the platelet count to normal following removal of the spleen Furthermore following the administration of cortisone to a patient with the disease it was not possible to demonstrate the presence of the platelet reducing factor in the blood although it was known to have been present previously

The conclusions which can be drawn from this notable addition to our knowledge are not clear at present It appears to have been demonstrated conclusively as all will agree that patients with idiopathic thrombocytopenic purpura have a circulating thrombocytopenic factor in the circulating blood presumably in the plasma and that it does not necessarily disappear when the platelet count increases following splenectomy They did demonstrate however that in the patient in whom the platelet count did return to normal following cortisone therapy the thrombocytopenic plasma substance was no longer demonstrable The authors

in some way inhibits platelet production by the megakaryocytes in the bone marrow—initially proposed by Frank in 1915 (*44*) and upheld by Dameshek and Miller (*45*). Recently a third theory has been advanced by Evans and his associates (*46*). They suggest that the thrombocytopenia is due to the action of an antibody produced by the spleen and other tissues which causes an increased destruction of blood platelets.

The theory of Kaznelson supported by Doan and his associates (*47*) that the blood platelets are destroyed by sequestration in the spleen and are destroyed there in excessive numbers has the following evidence in its favor. First, according to Doan (*47*), it can be shown that in these patients there are larger numbers of platelets entering the splenic artery than are leaving it via the splenic vein. Furthermore, when the spleen is removed from a patient with this form of purpura, it is possible to demonstrate phagocytosis of platelets in large numbers by the clasmatocytes in the spleen when vital staining is employed. Also, according to Doan, with the ligation of the splenic pedicle at operation for splenectomy in patients with idiopathic thrombocytopenic purpura, the blood platelets increase in number and blood clotting in the operative begins to return to normal within a few minutes. In addition, as emphasized by this observer, when adrenalin is given by the inter-arterial route or there is mechanical manipulation of the spleen, the sequestered platelets are released from the spleen and enter the blood stream.

The view originally proposed by Frank and championed by Dameshek and Miller (*45*) is that through a possible hormonal mechanism the megakaryocytes of the bone marrow are inhibited from normal platelet production and delivery. This theory is based on the following observations: although the blood platelets in the circulating blood are reduced, the bone marrow shows a normal or increased number of megakaryocytes, but there is evidence which is interpreted as indicating that these cells are actually producing a decreased number of platelets. Furthermore, they believe there is evidence that following splenectomy the megakaryocytes resume normal platelet formation. According to Dameshek and Estren (*48*) there is no indication that the spleen in this condition is destroying an excessive number of platelets. They state that in idiopathic thrombocytopenic purpura, before splenectomy, the megakaryocytes are mature, the cytoplasm is granular, the edges are distinct, and platelet formation is reduced. Following splenectomy, within 24 hours there is beginning platelet formation, and shortly thereafter this process is marked. It is concluded by these observers that splenectomy removes the hypersplenic organ containing the megakaryocyte-inhibiting material.

A third theory has recently been stressed by Evans and his collaborators (*46*). They suggest that in idiopathic thrombocytopenic purpura an autoantibody is produced by the spleen and other tissues which is responsible for an increased destruction of blood platelets in the circulating

cytes in the bone marrow is the most constant finding in essential thrombocytopenic purpura

The spleen is usually normal in size or slightly enlarged The average weight of six spleens removed surgically was 227 grams in the series reported by Nickerson and Sunderland (54) This organ may show hyperplasia and necrosis of follicles Megakaryocytes transported by the blood stream from the bone marrow may be found in the spleen and various other organs

The average weight of the spleen in 20 patients over 20 years of age was 232 grams the smallest weighed 103 and the largest 365 according to Hertzog (53) As the average normal weight in an adult is 150 grams he concludes that the spleen in this condition is not enlarged and is not palpable It is reported by Pemberton (55) that in a series of 57 splenectomies for thrombocytopenic purpura the average weight of the spleen was 201 25 grams He included in this series a spleen weighing 700 grams which had been removed from a 10 year old child

Grossly according to Stroebel Campbell and Hagedorn (56) the spleen is little enlarged if at all The average weight of the spleen in 22 of their patients with no recurrences reported in less than four years was 170 grams with a range from 70 to 300 grams In a group in which there were several recurrences after splenectomy the average weight was 174 4 grams with range from 100 to 300 grams In a group in which death occurred post operatively the average weight of the spleen was 165 grams with a range from 100 to 225 grams

Symptoms and Signs—The onset of the condition is most frequently characterized by the appearance of purpuric spots in the skin and bleeding from the mucous membranes without preliminary symptoms In some cases however there may be a history of bruising easily or epistaxis and in others the onset of the bleeding tendency may be preceded by an upper respiratory infection

The various terms employed to define the hemorrhagic lesions occurring in the different types of purpura have been defined as follows (57) 1 *Petechiae*—minute hemorrhages varying from the size of a pin point to that of a pin head in the skin and mucous membranes 2 *Ecchymosis* ("black and blue spot")—a purplish area in the skin resulting from hemorrhage up to the size of the palm of the hand 3 *Purpuric lesion*—synonymous with either petechia or ecchymosis 4 *Hematoma*—collection of effused blood in the subcutaneous tissues resulting in tumor formation 5 *Vibex*—linear ecchymoses and 6 *Suffusion*—large extravasation of blood without evident tumor formation

The purpuric eruption varies greatly in extent from a few scattered lesions the size of a pin point to large ecchymoses They are at first red and do not disappear on pressure the appearance is one of a superficial lesion which is not raised or indurated Fading is apparent within a few

suggest that the relief of thrombocytopenia by splenectomy may be due at least in part to a decrease in the rate of platelet destruction sufficient to permit the bone marrow to compensate for the platelet removing effect of the thrombocytopenic factor Pertinent comments indicating the need of a reassessment of the place of the spleen in this form of purpura have been made by Dameshek *(51)*

Of further interest is the demonstration that in infants born of mothers with idiopathic thrombocytopenic purpura there is certainly convincing evidence of some humoral substance in the circulating blood which undoubtedly passes through the placenta Such infants will manifest evidence of purpura with a diminished blood platelet count for several months following birth A comprehensive survey of 55 cases of congenital or neonatal thrombocytopenia with 50 references has been published recently by Robson and Walker *(52)*

Whatever theory is held to be the most plausible one at present it is clear to all that our knowledge concerning the role of the spleen and the spleen bone marrow relations is incomplete The recent studies cited however have added materially to our knowledge, and suggest that we are closer to a solution of the etiologic problems than ever before

Pathology —The most characteristic finding at necropsy in patients who have died of idiopathic thrombopenic purpura is the presence of widespread hemorrhage both gross and microscopic involving all organs including the brain The gross necropsy findings except for the extensive hemorrhages which are the cause of death according to Hertzog *(53)* are minor The hemorrhages are so widespread in 12 of the 36 of his patients that it was impossible to determine the principal site of the bleeding at necropsy In one third of his patients death was due to intracranial hemorrhages In a majority of the patients the hemorrhages were located beneath the dura mater and were diffusely scattered over the surfaces of the brain Occasionally intracerebral hemorrhages occur without an associated subdural hemorrhage The intracerebral and subdural hemorrhages may vary in size from petechiae to those massive in size In two of the 36 cases, extensive bleeding from the gastrointestinal tract predominated the hemorrhages varied from petechiae to massive ecchymoses involving the mucosa the walls and serosa of the stomach intestine and colon In one case the bleeding was chiefly from the mucosa of the renal pelvis and bladder

There is no evidence of a characteristic intrinsic pathology of the bone marrow in these cases The only pathological changes in the marrow are those which may be present as the result of chronic or acute hemorrhage No abnormal cells are observed The megakaryocytes are present in normal or increased numbers

It was concluded by Hertzog (53), however that apart from the widespread hemorrhages the presence of an increased number of megakaryo-

activity of a diseased spleen This point is well emphasized by Ehrlich and Schwartz (59) who report that in all but one of 13 cases of thrombocytopenic purpura with a palpable spleen the condition was secondary to some recognizable cause and hence the purpura was of the secondary type The causes in the 12 cases with palpable spleens were Laennec's cirrhosis three congestive splenomegaly two infectious mononucleosis two Gaucher's disease one lymphosarcoma one sarcoidosis one Hodgkin's disease one and hemolytic anemia one They observed one case with a spleen which could be palpated three centimeters below the costal margin in a 14 year old boy who apparently had idiopathic thrombocytopenic purpura and was relieved by splenectomy The spleen removed at operation weighed 210 grams and the pathologic diagnosis was "hyperplasia" I am in accord with the statement of Ehrlich and Schwartz (59) that the presence of a palpably enlarged spleen in thrombocytopenic purpura practically rules out the primary and allergic types

Blood Examination—There are certain characteristic findings always present in the blood of patients with this form of purpura which are *highly important from the standpoint of diagnosis* They are 1 a striking reduction in the number of platelets in the blood stream 2 a prolonged bleeding time 3 a normal clotting time and 4 non retractility of the clot

The blood platelets are usually reduced from the normal average number of 400 000 to 500 000 per cubic millimeter to 60 000 per cubic millimeter or less when active bleeding is present Counts as low as 5 000 to 10 000 per cubic millimeter are not uncommon and in some instances there may be *a complete disappearance of all platelets from the circulating blood* The degree of thrombocytopenia in our group of cases was usually pronounced when bleeding was present the platelet count was almost always below 50 000 per cubic millimeter and frequently much less

The bleeding time as determined by noting the interval required for a puncture wound of the lobe of the ear to cease bleeding is characteristically prolonged Normally when blood is absorbed from the wound on filter paper at minute intervals the bleeding persists for not longer than *three or four minutes* If the bleeding continues for over 10 *minutes* it is considered to be prolonged In some cases of this type of purpura it may continue for hours

The coagulating time is almost always normal but the clot when formed does not retract and express serum as it does normally The coagulation *time in our group of cases with rare exceptions* was within normal limits Occasionally however when there was a striking prolongation of the bleeding time there was also a moderate increase in the clotting time It was characteristic in almost all of our cases to observe that the clot when formed did not retract normally and express serum

days and this is followed by the various color changes observed in the familiar black and blue spot due to trauma Similar lesions occur in the various mucous membranes of the body

The bleeding from the mucous membranes varies from a slight oozing to hemorrhages so extensive as to result occasionally in a severe hypochromic anemia The bleeding is most frequently from the nose and mouth, but it may occur from the gastrointestinal tract with hematemesis and tarry stools or the urinary tract with hematuria, the uterus and into the various organs of the body including the brain which may be the immediate cause of death With cerebral involvement there is usually a severe and persistent headache Signs of either a hemiplegia or a meningitis may be present in some cases In this connection it is of interest to note that in all of our patients in whom a necropsy was performed there were hemorrhages in the brain

Profuse and prolonged uterine bleeding giving rise to a pronounced hypochromic anemia may be the sole evidence of the disease for a considerable period of time at the onset When this occurs in the absence of purpura the patients not infrequently consult the gynecologist who should never overlook the possibility that menorrhagia may be associated with various types of hemorrhagic states The importance of a routine blood examination in all women with uterine bleeding is urged by Reich (58) who reports 15 cases in which the initial or predominating symptom was abnormal uterine bleeding in association with thrombopenic purpura

Pulmonary bleeding and hemorrhage into the joints are rare Fever ranging from 100 degrees to 102 degrees is not infrequently present in the acute cases, and when the anemia is severe A febrile rise is rarely observed in the mild cases or in the chronic forms of the disease unless the bleeding is intense or some complication exists

The important findings on physical examination are evidence of bleeding into the skin and from the mucous membranes a variable degree of pallor usually mild but depending upon the amount of blood which has been lost and occasionally a slightly enlarged spleen Gross splenomegaly is never seen and when present it should at once excite the strong suspicion that the purpura is of the secondary type Likewise it should also be emphasized that the lymph nodes do not show generalized enlargement in idiopathic thrombopenic purpura

Occasionally the edge of the spleen may be felt 2 or 3 centimeters below the left coastal margin but it is never greatly enlarged Whenever the spleen is palpable and especially when there is gross enlargement one should consider the possibility that the thrombocytopenia may be of the symptomatic or secondary type due to marrow replacement by lymphosarcoma leukemia reticulo endothelial or carcinoma cells, or fat fibrous tissue or bone or that it might be due to the hypersplenic

The anemia if present in idiopathic thrombopenic purpura is usually not of the normochromic or macrocytic types but is more commonly of the hypochromic variety. Although normochromic or macrocytic anemia may occur in patients with this variety of purpura it is usually fleeting in nature and if the anemia is persistent it usually changes in character to the hypochromic microcytic type. Every effort should be made to eliminate the possibility of a food or drug idiosyncrasy as the cause of the purpura. It may be due in some instances to certain articles of diet or drugs such as the sulfonamides sedormid quinine gold and various others mentioned in the section dealing with allergic thrombopenia.

It is of special importance in the diagnosis of this disease to note if the spleen or the lymph glands are enlarged. Although the tip of the spleen is occasionally palpable in patients with idiopathic thrombopenic purpura a gross enlargement should always suggest a secondary or symptomatic type of the disease. Likewise a generalized lymphadenopathy is not seen in the idiopathic type and its presence points to the possibility that the patient has the secondary variety.

The diagnostic essentials listed by Wiseman Doan and Wilson (43) should always be given serious consideration before the diagnosis of idiopathic thrombocytopenic purpura is made. They are as follows

1 There must be spontaneous purpura and/or free bleeding from the mucous membranes

2 The blood platelets must be substantially decreased in numbers that is less than 100 000 per cubic millimeter of blood

3 The clotting time and prothrombin time must be within normal limits

4 The anemia and leukocyte count must not be out of proportion to the amount of bleeding

5 There must be no pathologic cells in either the blood or the bone marrow

6 There must be no recent history of the ingestion of drugs or the occurrence of those diseases known occasionally to produce thrombocytopenia

7 There must be no appreciable enlargement of the spleen or lymph nodes

Treatment —In the treatment of idiopathic thrombocytopenic purpura the following measures should be given consideration 1 blood transfusions 2 the use of cortisone and adrenocorticotrophic hormone 3 splenectomy and 4 other therapeutic agents which have been considered from time to time

It should be kept in mind that this disease is characterized by spontaneous remissions and hence therapeutic claims based on short time observations of a relatively few patients should be accepted with caution

The prothrombin consumption test as introduced by Quick and Favre Gilly (60) is a measure of the amount of plasma thromboplastin which reacts with prothrombin. The value is obtained by estimating the prothrombin before and after clotting is complete. Normally, one hour after coagulation has occurred, about 20 per cent of the prothrombin present remains in the plasma, in hemophilia and thrombocytopenia about 70 per cent remains (61).

Additional information concerning the abnormal tendency to bleed may be obtained from the tourniquet test. This may be performed by applying a blood pressure cuff and inflating it to the point where the venous return but not the arterial flow is obstructed. In thrombopenic purpura petechiae or ecchymoses usually appear below the location of the tourniquet in from three to 10 minutes. Determination of the capillary resistance as measured by a special suction apparatus, is considered by some to be superior to the tourniquet test.

An anemia may be present after acute or chronic hemorrhage or a combination of both. It is very slight in a majority of cases. The color index is ordinarily below 1.0, slight anisocytosis and poikilocytosis are commonly present and there is frequently a slight leukocytosis with an increase in the polymorphonuclear cells. Occasionally normoblasts and cells showing diffuse polychromatophilia and stippling are seen. The mean corpuscular hemoglobin concentration is 30 per cent or less and the mean corpuscular volume is usually below 86 cubic microns. After staining with cresyl blue there is often an increase in the number of reticulocytes observed when a definite anemia is present. If the anemia is entirely due to chronic hemorrhage, it will be of the hypochromic microcytic type. On the other hand, if acute hemorrhage of considerable extent has occurred, it may be of the normocytic or even macrocytic type.

In a great majority of cases the leukocyte count is within normal limits and there is no disturbance in the differential count. It has been pointed out to me by Dr. Jose Baez Villaseñor, after studying our group of cases, that an eosinophilia varying from four to 34 per cent may be present in these patients following widespread cutaneous hemorrhages.

Differential Diagnosis.—This condition may be simulated by various other types of purpura. In the past the failure to separate it from other similar conditions has led to confusion concerning the prognosis and the efficacy of the various types of therapy. It should be remembered that this condition is primarily one which is present in children and in young adult life. The diagnosis of the idiopathic type of thrombocytopenic purpura should be made with a great deal of caution in older persons as a relatively small per cent of the cases occur after 40 years of age. One should beware of making this diagnosis in the presence of a persistent leukopenia, as this condition is more often associated with other blood dyscrasias, as aplastic anemia or subleukemic leukemia.

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The diagnostic essentials listed by Wiseman Doan and Wilson (*43*) *should always be given serious consideration before the diagnosis of* idiopathic thrombocytopenic purpura is made. They are as follows

1 There must be *spontaneous purpura and/or free* bleeding from the mucous membranes

2 The blood platelets must be substantially decreased in numbers that is less than 100 000 per cubic millimeter of blood

3 The clotting time and prothrombin time must be *within normal* limits

4 The anemia and leukocyte count must not be out of proportion to the amount of bleeding

5 There must be no pathologic cells in either the blood or the bone marrow

6 There must be no recent history of the ingestion of drugs or the occurrence of those diseases known occasionally to produce thrombocytopenia

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coated with silicone Platelet survival was estimated by noting the return of the platelet count to pre transfusion levels By this method they concluded that platelet survival in patients with idiopathic thrombocytopenic purpura was 24 hours or less whereas in other conditions as acute leukemia it was four to six days They conclude from their experience employing polycythemic donors with platelet rich blood and using silicone coated syringes and needles that the platelet transfusions were beneficial in both acute and chronic thrombocytopenias in controlling acute hemorrhagic episodes and in preparing patients for surgery The chief difficulty with this method from a practical standpoint would be in having an untreated polycythemic patient available when needed to serve as a donor and provide platelet rich blood

In general it is my conclusion that blood transfusions are indicated in patients with this type of purpura in treating shock and any anemia which may be present They may be of some service in increasing the total number of blood platelets significantly and thereby controlling hemorrhage The available evidence however does not provide sufficient evidence to indicate that there is satisfactory control of this type of bleeding with such a therapeutic measure

Adrenocorticotrophic Hormone and Cortisone —Sufficient studies have now been made on the administration of these therapeutic agents to state that they are of great value in treating this type of blood disorder Reports of their favorable effect on patients with this type of purpura have been made by various authors *(66 67 68 69 70)*

Within three to seven days there is a definite increase in the platelets of the circulating blood the bleeding time decreases rapidly to normal and the tendency to bleed abnormally is controlled in almost all patients For example in 15 of our patients at the Simpson Memorial Institute with this disorder there was an entirely satisfactory response to either ACTH or cortisone in all but one of the patients or 93 per cent Occasionally a response does not occur until the end of the second week of treatment A patient should be treated for at least 10 days before it can be said that this form of therapy has been given a fair trial If there is no evidence of a response in that length of time one is not likely to occur with further treatment

After the therapy had been given for several weeks and the blood condition controlled satisfactorily the medication was then omitted and the patient kept under observation In about 60 per cent of the patients there was a relapse within a variable period of a week to a month or more Again the medication was given and in five of the seven who relapsed it was possible to induce promptly a second satisfactory remission preliminary to splenectomy In all seven patients a splenectomy was performed with excellent immediate results In one patient there was absolutely no response to adequate doses of either ACTH or cortisone but an entirely

Undoubtedly the apparent good results of some forms of treatment have been based entirely on improvement which has occurred as a result of variation in the spontaneous course of the disease

Blood transfusions may be indicated in these patients for three reasons namely 1 to treat imminent shock 2 as a means of restoring to the hemoglobin and red blood cells of the peripheral blood more rapidly to normal when they had been reduced as the result of associated acute and chronic hemorrhage, and 3 and possibly as a method of increasing the number of blood platelets in the circulating blood and thereby controlling the hemorrhagic tendency

There can be no question about the advisability of using whole blood transfusions freely for the purpose of treating shock or when this condition is impending Five hundred cubic centimeters should be given promptly and if the patient's condition does not improve at once this should be repeated at frequent intervals until satisfactory results are obtained

It is not uncommon to have an anemia due to hemorrhage present in patients with this type of purpura but usually it is not severe Nevertheless if the hemoglobin of the circulating blood falls below 11 grams per 100 cc of blood (70 per cent) a sufficient number of blood transfusions should then be given to restore the level of the hemoglobin and red blood cells to normal Furthermore if there is reason to believe that there has been chronic hemorrhage iron in the form of ferrous sulphate should be given in doses of 0 3 gram (5 grains) in enteric coated tablets three times daily before meals

There is less agreement concerning the ability of blood transfusions to increase the number of circulating blood platelets and thereby diminish the bleeding time It is recommended that "stored bank blood *not* be used for this purpose as it is known that within a few hours after the blood is drawn the platelets agglutinate and are probably ineffective in performing their normal function relating to clotting The platelets are known to fall to less than 100 000 per cubic millimeter in 24 hours in stored blood according to the observation of Drew and Scudder (*62*) and to about 40 000 per cubic millimeter in three days They remain however at a fairly constant level of 40 000 per cubic millimeter even after 14 days of storage in a citrate dextrose mixture (*63*)

It has been concluded by Lawrence Valentine and Adams (*64*) that direct blood transfusions fail to raise the platelet level in the circulating blood appreciably Recently however Hirsch and Gardner (*65*) reported that when platelet rich blood from polycythemic donors is introduced into patients with idiopathic thrombocytopenic purpura and patients with other types of thrombocytopenia the platelet count could be increased by an average of 90 000 per cubic millimeter The blood was collected from polycythemic patients using needles and syringes

cedure will cure permanently about 80 per cent of all patients and perhaps more The mortality rate in the future will no doubt be diminished by preparing the patient for operation with cortisone and hence there should rarely be cause for abnormal bleeding Furthermore the results in the future should be better now as in some instances the cause for failure is known to be the presence of accessory spleens Splenectomy with careful exploration for accessory spleens is recommended therefore in all patients with this disease provided they cannot be controlled for an indefinite period with cortisone

In summary therefore a patient with such a condition should be treated with multiple blood transfusions if shock is present or impending Cortisone should be given until the blood platelets and the bleeding time reach normal limits It should then be discontinued and the patient observed If relapse occurs cortisone should be given again until the

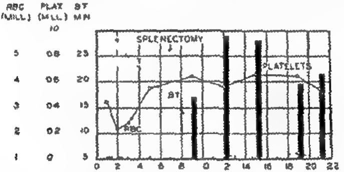

Fig 52 —Changes in the blood of a 15 year old girl with idiopathic thrombocytopenic purpura A few purpuric spots had been present over her body at intervals for 6 years but symptoms did not appear until the onset of her menstrual periods at which time there was excessive loss of blood with the resultant development of a hypochromic anemia The red blood cell count had decreased to 3 1 millions per cubic millimeter and the hemoglobin to 41 per cent (6 4 grams) When first seen the platelet count was 8400 per cubic millimeter and the bleeding time exceeded 25 minutes at which time the bleeding was still profuse Following two blood transfusions the spleen was removed This was followed by a prompt cessation of the bleeding a striking increase in the blood platelets and a return of the red blood cell count and hemoglobin to normal When seen 3 months after the operation the patient had no complaints and the red blood cell count was 5 5 millions per cubic millimeter the hemoglobin 80 per cent (12 5 grams) the bleeding time 2 minutes and the platelets 249 000 per cubic millimeter

platelets and bleeding time have been restored to normal which can usually be accomplished Splenectomy should then be performed and a careful search for accessory spleens made If present they should of course be removed When this is done although it is said that a cure is effected in only 80 per cent of the patients my impression is that the percentage of cure is greater

Prognosis —Past experience indicates that in about 80 per cent of the patients splenectomy will result in a prompt remission whereas in about

satisfactory result was obtained with splenectomy In one patient there was a failure to respond to ACTH but the response attained with cortisone was satisfactory In about 40 per cent of all the patients there was a sustained remission after the medication had been administered fo only about three weeks and then stopped These patients have remained in a satisfactory condition to date for periods as follows one for 16 months two for 12 months one for nine months, and one for seven months The patient who has had the long remission of 16 months went through a normal pregnancy and gave birth to an apparently healthy infant

It is anticipated therefore, that these therapeutic agents will produce favorable effects in patients with this type of purpura and will be of great value in 1, preparation for splenectomy as the bleeding time can be brought to normal and the tendency to abnormal bleeding entirely controlled Hence the operative mortality which has been in the vicinity of 5 per cent should be greatly reduced 2, In some patients apparently a long remission may result and splenectomy averted

A satisfactory dosage of ACTH is 25 milligrams four times daily, given intramuscularly, or cortisone given orally, 75 milligrams four times daily equally spaced in the 24 hours The medication should be continued until the platelet count is within normal limits and the bleeding time is no longer prolonged which is usually a period of about two to three weeks I have favored the use of cortisone because the possibility of insufficiency of the adrenal cortex being eliminated the medication can be taken orally and some cases have responded to cortisone when ACTH has failed Patients receiving this therapy have been placed on an 800 milligram low sodium diet No untoward effects from the treatment have been observed

The mode of action of ACTH and cortisone in idiopathic thrombocytopenic purpura is obscure, and any views expressed at this time concerning such a mechanism must be regarded as purely speculative It may be that they interfere with immune reactions responsible for the thrombocytopenia Their action therefore might be to curtail the production of antibodies formed by lymphatic tissues If this were correct ACTH and cortisone might then be assumed to act by causing a regression in the lymphoid tissues and hence causing a decrease in the formation of such humoral bodies The fact that roentgen ray therapy which acts on lymphatic tissue is not highly beneficial in these hematologic disorders is not entirely in accord with this theory It may be however that despite the action of this agent on lymphoid tissues it does not accomplish identical effects as those produced by ACTH or cortisone

Splenectomy —Unless further studies indicate that patients with this condition may be controlled with cortisone or ACTH perhaps given at repeated intervals the treatment of choice is splenectomy This pro-

cedure will cure permanently about 80 per cent of all patients and perhaps more The mortality rate in the future will no doubt be diminished by preparing the patient for operation with cortisone and hence there should rarely be cause for abnormal bleeding Furthermore the results in the future should be better now as in some instances the cause for failure is known to be the presence of accessory spleens Splenectomy with careful exploration for accessory spleens is recommended therefore in all patients with this disease provided they cannot be controlled for an indefinite period with cortisone

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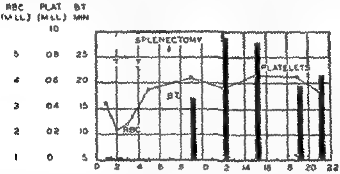

Fig 52 —Changes in the blood of a 13 year old girl with idiopathic thrombocytopenic purpura A few purpuric spots had been present over her body at intervals for 6 years but symptoms did not appear until the onset of her menstrual periods at which time there was excessive loss of blood with the resultant development of a hypochromic anemia The red blood cell count had decreased to 3 1 millions per cubic millimeter and the hemoglobin to 41 per cent (6 4 grams) When first seen the platelet count was 8400 per cubic millimeter and the bleeding time exceeded 25 minutes at which time the bleeding was still profuse Following two blood transfusions the spleen was removed This was followed by a prompt cessation of the bleeding a striking increase in the blood platelets and a return of the red blood cell count and hemoglobin to normal When seen 3 months after the operation the patient had no complaints and the red blood cell count was 5 5 millions per cubic millimeter the hemoglobin 80 per cent (12 5 grams) the bleeding time 2 minutes and the platelets 249 000 per cubic millimeter

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TABLE XXVII

H A NO 324719 AGE 34—IDIO THROMBOCYTOPENIC PURPURA

Date	HB	R B C	Platelets
November 2 1933	58	4 2	+
November 7 1933	62	3 7	+
November 17 1933	76	4 1	+
December 4 1933	75	4 6	+
December 6 1933		Splenectomy	
December 14 1933	71	3 5	++++
December 29 1933	67	4 4	++++
February 7 1934	90	4 5	++++

TABLE XXVII—H A No 324719 The patient a 34 year-old male entered the Simpson Memorial Institute in November 1933 with the history that for three years he had suffered from severe repeated epistaxes there having been considerable loss of blood several times a week for three years During this interval he had experienced the symptoms of anemia namely weakness ease of fatigue dyspnea and palpitation The platelets of the circulating blood were greatly reduced and the bleeding time was 35 minutes Following splenectomy there was a prompt rise in the blood platelets the bleeding ceased and the blood returned to normal When last seen four years after the operation the patient s blood was entirely normal and there was no evidence of purpura

30 per cent if conservative measures are carried out at least transient satisfactory improvement will follow The results attained by splenectomy at the Mayo Clinic and reported in 1949 by Stroebel Campbell and Hagedorn (56) are as follows in a group of 59 adults with idiopathic thrombocytopenic purpura who were treated by splenectomy 84 7 per cent had a satisfactory prompt response 10 2 per cent were unimproved and 5 1 per cent died in the immediate postoperative period A comparable group of 26 adults who refused operation were observed and in 42 3 per cent there was an immediate spontaneous remission lasting about six months 26 9 per cent continued to have some purpura and 30 8 per cent succumbed within three months with cerebral hemorrhage

It is the opinion of Wintrobe (71) that the chances of continued recovery following conservative or medical treatment are less than one out of three but following successful splenectomy the chances for continued recovery would be almost three out of four in cases in which there had been only one episode of bleeding and somewhat better than one out of two in cases in which several episodes have occurred He states however that the writer s subsequent experience suggests that these are conservative estimates

It is concluded by Wiseman Doan and Wilson (72) that if the bleeding is severe enough to warrant surgery and the splenectomy is not performed the mortality will be 30 per cent Of those operated upon not more than three per cent will have recurrences

In the third of a series of reports issued from the Spleen Clinic of the Presbyterian Hospital in New York City (73 74 75) Elliott presents

figures dealing with the treatment of thrombocytopenic purpura by means of splenectomy as follows after splenectomy in 62 patients with idiopathic thrombocytic purpura followed for a period of two months to 20¹/ years the operation failed to improve 23 per cent of the patients or it was of dubious benefit and in 77 per cent it was of marked benefit or the condition completely arrested When these results are compared with those in 25 patients in whom the operation was not done the results are obviously in favor of the operation In the group in whom splenectomy was not performed and who were followed for a period varying from one month to 15¹/₂ years the results were as follows in 64 per cent the treatment failed or was of dubious benefit in 28 per cent there was a marked improvement and in 8 per cent the disorder was completely arrested In the group in whom splenectomy was done there were no operative or hospital deaths but subsequently five or 8 3 per cent died after a temporary arrest of the disease In the group in whom the operation was not done there were three deaths or 12 per cent

In summarizing one could say that in patients in whom splenectomy was done the results were good in 77 per cent and poor in 23 per cent in those without the operation the results were good in 36 per cent and poor in 64 per cent The conclusions of Elliott (75) are essentially as follows splenectomy remains the most effective form of treatment of idiopathic thrombocytopenic purpura but an appreciable number of disappointing results must be anticipated especially in the older age groups He also warns that a long term follow up is particularly important for a considerable number of patients improve only temporarily and fatal recurrences have been known to occur as late as two years after the operation

In our own series of 41 patients who had a splenectomy performed 34 are living and well over a period of as long as 15 years postoperatively Four of the 41 patients or 9 7 per cent succumbed to the operation but it should be emphasized that three were in extremely poor condition when the operation was performed and the third had an accessory spleen

The mortality for the operation in most of the reported series is about 5 0 per cent including the acute and chronic types In my opinion however with improved surgical technic and the preoperative use of cortisone this unduly high figure may be appreciably lowered One also must take into consideration that in these patients the outlook is always uncertain If conservative measures are used the threat of a recurrence must be kept in mind sometimes complicated by hemorrhage and the possibility must be considered that an extensive hemorrhage may occur in some vital organ as the brain On the other hand while splenectomy offers the best possibility of a cure it is not possible to predict with certainty that the results will be satisfactory in any given patient

Miscellaneous Forms of Treatment —As this disease is characterized by spontaneous remissions it is not surprising that many forms of therapy

have been claimed to be beneficial. In my opinion, however, it has not been demonstrated that any of the following therapeutic agents produce worth-while results: the older remedies such as sulfuric acid, ergot, turpentine, iodine, and coal tar (76), heliotherapy, irradiation of spleen (77), ultraviolet light (78), viosterol (79), vitamin P (80), ascorbic acid (81), foreign protein injections (82), high protein diet (83), fat-soluble "T" factor (84), anterior lobe of pituitary (85), parathyroid extract (86), liver extract (87), kephrine hydrochloride (88), toluidine blue (89), congo red (90), snake venoms (91, 92) and removal of foci of infection.

Course of the Disease and Prognosis.—The spontaneous course of the disease is accurately expressed in the words of Wintrobe and his collaborators (38) as follows: "It is evident that the first manifestations of purpura hemorrhagica may be mild or fulminating. The initial symptoms may disappear never to recur, or they may progress without interruption and cause grave anxiety. Relapses or recurrences may take place at unpredictable times and may be more serious or less acute than the original episodes. So variable is the course of this disease that it is impossible to predict with any degree of assurance what the subsequent progress of a given patient is likely to be."

It is not uncommon for patients, when treated medically, to recover immediately from the first episode of bleeding, but only about one quarter of the patients remain continuously in good health. In the group studied by Wintrobe and his associates, about three quarters of the relapses occurred within four years, but in some instances there may be a much longer interval of health followed by a relapse. From the data presented by these authors, it is possible to state that if one episode of bleeding has occurred, the chances of continued recovery are less than one out of three for patients treated medically. In untreated patients and those treated medically, therefore, it must be conceded that a chronic state is likely to develop with varying degrees of incapacitation. In any given case there are no reliable data which enable one to predict if a recurrence will occur and when it might be expected. In Wintrobe's series of 18 cases there was a variable period of from one month to 26 years between the first and second bleeding episodes.

In our own group of 91 cases studied by Dr. José Báez Villaseñor from the standpoint of prognosis, the conclusion was reached that spontaneous remissions occurred commonly and in some instances are complete and permanent. The usual course of the disease is one characterized by recurrences which Dr. Báez thought had a tendency to be less severe than the original attack. Opinion on this latter point, however, varies. He did not think that age or sex influenced the spontaneous clinical course or the progress of the condition following splenectomy.

Many forms of therapy have been tried in this disease and there has been a considerable difference of opinion about the proper course to pursue. This has been due largely to the following reasons: 1. because the

disease tends to follow a course characterized by spontaneous remissions and exacerbations which make evaluation of therapy difficult especially if only a few cases are studied in one group and 2 errors in the diagnosis which have led to splenectomy or other types of treatment in patients with some other type of purpura than the idiopathic variety

Accessory Spleens and Other Causes of Failure Following Splenectomy —In a study of 14 patients who had been operated upon for idiopathic thrombocytopenic purpura and then either failed to improve or made a recovery and then relapsed it was found by Rosenthal Vogel Lee and Lipsay (93) that accessory spleens were present in only four patients The presence or absence of the accessory spleen was determined by thorotrast visualization by operation or by post mortem examination They conclude that the studies by Watson and Moir (94) and those by Curtis and Movitz (95) "reveal an unconvincing body of evidence in relation to this subject On the other hand they conclude that if a complete hematological and clinical remission follows splenectomy in a patient with this disorder and then there is a recurrence of purpura one should be suspicious of an accessory spleen or spleens as the cause of the relapse They recommend visualization by means of thorotrast using a technic similar to that employed by Yater and Otell (96) as a helpful method to determine the presence and location of such spleens In their opinion a majority of patients do not have accessory spleens which are responsible for recurrences of purpura following splenectomy

If there is a recurrence of purpura in this type of blood disorder and a failure to demonstrate the presence of accessory spleens either by thorotrast visualization operation or at post mortem what then could be the basis for the recurrence? This is answered in part at least by the statement of Doan (97) who believes that such a recurrence may be attributable to a generalized hyperplasia of hyperfunctioning reticuloendothelial cell phagocytes which may occur in the liver and lymph nodes Furthermore this author is of the opinion that a hypersplenic relapse may be precipitated by as little as five grams of tissue having such a trait If this is correct and it is difficult to prove beyond a question of a doubt it is not surprising then that such a cause might be overlooked by thorotrast visualization and by the surgeon at operation

It is reported by Elliott and Turner (98) that during splenectomy in 68 patients with idiopathic thrombocytopenic purpura accessory spleens were searched for in all instances and found in 17 or 25 per cent of the patients In seven cases they were in the splenic pedicle in two in the gastrosplenic ligament in one beneath the tail of the pancreas in three in the retroperitoneum over the left kidney and in four the location was not given They conclude that not all cases of recurrences are due to accessory spleens not apparent or overlooked at operation In their opinion however it does not lessen the advisability of operating again upon such patients in carefully selected instances It is of interest to note that in

the 17 cases in which accessory spleens were removed at the initial operation there were 13 successful results and four failures. Hence the over all results (about 75 per cent showing marked improvement or complete arrest) did not differ from those in the remainder of the series studied by them.

Idiopathic Thrombocytopenic Purpura in Children.—Recently Newton and Zuelzer (*99*) have emphasized that the syndrome of idiopathic thrombocytopenic purpura in children differs from that in adults in some respects. About 85 per cent of the group of 47 children studied by these observers were eight years of age or younger. In a majority of the cases the disorder appeared to be a benign self limiting condition of short duration. It differs from the idiopathic thrombopenic purpura seen in adults as there is no sex predilection. It could not be demonstrated that there was a definite relationship between the condition and allergy or infection of any type. Bone marrow aspirations were done in 30 cases but uniform changes could not be demonstrated. In 11 cases the megakaryocytes were increased, in four they were thought to be normal, and in eight a decrease was evident. A majority of patients showed evidence of immaturity of the megakaryocytes and evidences of failure of these cells to form platelets normally but these findings were not invariably present. It is their opinion that adequate criteria for splenectomy in idiopathic thrombocytopenic purpura in children have not been established. In chronic cases splenectomy may or may not result in a cure. They believe that removal of the spleen in this condition, when it occurs in children, should probably be employed only in cases of uncontrollable bleeding or chronic recurrent purpura. They make no recommendations concerning the use of cortisone as a therapeutic agent but state that it will be the subject of a later report.

Idiopathic Thrombocytopenic Purpura in Pregnancy.—There has been an increasing interest in purpura during pregnancy since the initial case was reported by Barnes in 1867 (*100*). In extensive reviews by Robson and Davidson (*101*) and Barnes and Doan (*102*), it is apparent that such a complication presents a definite hazard to both the mother and child. It is estimated that the infant mortality is about 25 per cent and the maternal mortality 8 to 10 per cent. There is no indication that pregnancy is a factor in producing the disease. The fact that it occurs most frequently in females below the age of 30 and that this is also the age of greatest frequency of pregnancy probably explains why the two conditions co-exist.

In the opinion of Barnes and Doan (*102*) if the diagnosis of idiopathic thrombocytopenic purpura is firmly established, the presence of pregnancy does not alter the hematological indications for splenectomy. They believe that the hemorrhagic state represents a greater hazard than does the operation of splenectomy regardless of the trimester of pregnancy. It is emphasized by Barnes (*103*) and others (*104, 105*) that although the

purpuric state does not necessarily influence blood loss antepartum and intrapartum hemorrhage nevertheless remains a constant risk and intra uterine death of the fetus may occur from retroplacental hemorrhage *Furthermore they believe that splenectomy even with a thorough search* for accessory spleens should not precipitate labor but they urge gentleness of intra abdominal manipulation in order to prevent the onset of uterine contractions

The presence of thrombocytopenic purpura in the child born of a mother with the disease is of considerable interest as it indicates the presence of a hormone like substance in the circulation of the pregnant woman This apparently crosses the placenta and acts upon the fetus to produce a similar type of purpura According to Slaughter and his associates (*106*) *every acceptable case in the literature has revealed that when the mother* has had thrombocytopenic purpura at delivery the fetus also has had this condition Furthermore they state that all of the surviving infants completely recovered after their removal from the influence of their maternal circulation On the other hand it is reported by Epstein *et al* (*107*) that only *one half* of the children of mothers with idiopathic thrombocytopenic purpura who are born living have congenital thrombocytopenic purpura Within a few months however their platelet counts increase to normal and almost invariably remain elevated

In my own opinion the presence or absence of pregnancy should not alter the decision as to whether or not splenectomy is indicated In view of the excellent preliminary reports from the use of ACTH and cortisone in purpura of this type however one should give this form of therapy consideration as a temporary expedient which might carry the patient through to term At present I do not know of any ill effects in pregnant women due to these preparations Studies by Jailer (*108*) are of interest in this connection

Thrombocytopenic Purpura of the Newborn—In recent years thrombocytopenic purpura *has been reported in infants at birth and in some of* these patients it has been associated with thrombocytopenic purpura in the mother

The subject has been reviewed by LaDriere (*109*) This author recognizes that purpura which occurs during the first two weeks of life may be associated in some patients with leukemia aplastic anemia congenital syphilis erythroblastosis sepsis and sensitivity reactions due to known toxins

Of greatest interest however is the type of purpura which occurs at birth *or shortly thereafter in infants born of mothers who have idiopathic* thrombocytopenic purpura As stated by LaDriere (*109*) " it is probable that some responsible agent passes from the mother to the infant via the placenta" This observer reports a case of thrombocytopenic purpura in the newborn in which the mother had previously been splenec

tomized He states that this is the forty sixth reported instance of this condition and the eighth time a report has appeared that a mother, who had previously been subjected to splenectomy, gave birth to one or more infants with purpura during the first 14 days of life This is convincing additional evidence that the spleen alone is *not* the sole causative factor *in the* production of idiopathic thrombocytopenic purpura Perhaps the causative agent arises in some other cells of the body such as those of the reticulo endothelial system or the lymphocytes

Needless to say, the prognosis for the infant is much better in this form of purpura which is transmitted from the mother to the fetus via the placenta If the infant survives the first month of life, the prognosis for complete recovery is good On the other hand if the thrombocytopenic purpura is secondary to some condition as leukemia or aplastic anemia then, of course the prognosis is not better than that of the primary disease

Treatment of the congenital form is entirely symptomatic, and complete recovery can usually be anticipated It would be of interest to observe however if appropriate doses of ACTH or cortisone expedited the recovery of such patients

It should be kept in mind as stated by LaDriere (*109*) that all infants born of mothers who give a history of purpura do not always have purpuric manifestations According to this author approximately 70 per cent of infants born under these circumstances fail to develop bleeding tendencies during the newborn period Some of these, however will have thrombo penia without evidence of purpura

THROMBOTIC THROMBOCYTOPENIC PURPURA

Definition —A syndrome associated with disseminated arteriolar occlusions occurring at all ages but more commonly in the female sex characterized by an acute onset fever hemolytic anemia thrombocytopenic purpura and by bizzare mental and neurological manifestations With rare exceptions the disease is progressive and fatal

The condition was first described in 1925 by Moschcowitz in a publication with the title Acute Febrile Pleiochromic Anemia with Hyaline Thrombosis of Terminal Arterioles and Capillaries (*110*) The name Thrombotic Thrombocytopenic Purpura was given to the disorder by Singer and his associates (*111*) A recent review has been published by Meacham *et al* (*112*) which contains references to the previously published literature dealing with the disorder

Age and Sex Incidence —The condition has been observed in both the white and Negro race It occurs from youth to old age the reported range being from nine to 66 years Three of the cases observed by Singer Bornstein and Wile (*111*) were under 16 years of age These same observers report that the ratio of females to males is 5 1 but they consider that at present the number of cases observed is too small to draw definite

conclusions concerning the sex distribution The malady is rare there being only 20 cases reported up to 1950

Etiology and Pathology.—At necropsy the striking finding is the presence of innumerable thrombotic lesions in the capillaries and small arterioles throughout the body which Singer and his associates (*113*) consider to be made up principally of platelets with a small amount of fibrin but no erythrocytes In the lungs there may be megakaryocytic thrombi There is proliferation in varying degree of the endothelial lining of the vessels The possibility has been considered that the condition is related to disseminated lupus or polyarteritis

It has been suggested that the loss of platelets in the multiple thrombi results in a depletion of the bodies in the circulating blood and hence accounts for the thrombocytopenia (*114*)—a suggestion which is appealing in its simplicity The increase in the megakaryocytes in the bone marrow could then be considered as compensatory According to Singer Motulsky and Shanberge (*113*) the anemia is due to a hemolytic process unaccompanied by evidence of autoimmunization as it is not possible to demonstrate autoagglutinins in the circulating blood and the Coomb s test is negative

It is the opinion of Meacham and his associates (*112*) that the primary lesion in the disease is the degenerative changes in the blood vessels and hence the condition is related to the so called collagen diseases They report the occurrence of aneurisms in the arterioles and precapillary vessels in their patients It is their belief that the occlusive lesion is the result principally of changes in the vessel walls and that it is not due primarily to a deposition of platelets Furthermore they suggest that the thrombocytopenia may be attributed to a process similar to that which occurs in idiopathic thrombocytopenic purpura and hence is concerned probably with some abnormal process in the spleen It is stated by these investigators that the cause of the hemolytic anemia is unknown

Symptoms Signs, and Course of the Disease.—The characteristic features of this disease are the presence of a thrombocytopenic purpura a hemolytic anemia and signs due to the occlusion of small arterioles often producing bizarre neurological manifestations and mental changes Such a combination of symptoms and signs is pathognomonic of this syndrome as it is not observed in any other disorder Its clinical evidences are summarized by Singer Bornstein and Wile (*111*) as follows an acute febrile illness characterized by 1 petechiae and ecchymoses *thrombocytopenia* prolonged bleeding time and poor clot retraction 2 severe anemia out of proportion to the observed blood loss 3 a mild acholuric jaundice hepato splenomegaly 4 bizzare and intermittent mental and neurologic symptoms and signs and 5 transient leukemoid reactions in the blood

Prognosis and Treatment.—With rare exceptions, the disease has a rapidly down hill course and terminates fatally. A long remission has been reported in one patient following splenectomy (*112*) but in a few other instances this form of treatment did not alter the course of the disease. It is true that splenectomy has not received a fair trial and further consideration should be given to it. ACTH has been used in a single patient and transient improvement observed, although relapse occurred while the treatment was being given. It is possible that this form of therapy, when administered in larger doses, might be helpful or perhaps cortisone in doses of 100 milligrams three times daily, might be of benefit.

SYMPTOMATIC THROMBOPENIC PURPURA

Introduction.—This type of the disease presents the clinical picture of bleeding from the mucous membranes, purpura, and a reduction in the number of circulating blood platelets. It differs from the idiopathic type in that it is due to a recognizable cause. In some instances the mechanism of the thrombopenia is considered to result from an actual diminution in the number of megakaryocytes, the precursors in the bone marrow of the blood platelets, and in others it is assumed that, although the megakaryocytes are present in normal numbers, they undergo maturation slowly and hence yield platelets to the blood stream at a diminished rate.

This variety of purpura may be divided conveniently into four main divisions, namely, 1, the type associated with various blood diseases, 2, those secondary to infections, 3, those associated with defects in the bone marrow, namely, a decrease in the number of megakaryocytes such as is seen following the invasion of the bone marrow by cancer, and 4, allergic purpura which is associated with sensitivity to drugs, food, and possibly other allergens.

It is of the utmost importance from the standpoint of therapy to investigate thoroughly every patient with thrombopenic purpura to determine if it is secondary to a known cause. If the patient has the idiopathic type, it is likely that benefit will be derived from splenectomy. On the other hand, if the condition is classified as the secondary or symptomatic form, splenectomy is then contraindicated, for the patient will be subjected to an operation which could not possibly be of benefit. The treatment of this variety of the purpura should be directed toward its fundamental cause, which varies in different patients.

PURPURA SECONDARY TO VARIOUS BLOOD DYSCRASIAS

All of the manifestations of true thrombopenic purpura may occur as a part of the picture of extensive involvement of the hematopoietic

system with a primary disease. It most frequently accompanies the leukemias especially the acute varieties and aplastic anemia but it may also be observed in pernicious anemia sickle cell anemia hemolytic anemia *in myelosclerosis* and *occasionally in Banti's disease* Hodgkin's disease Gaucher's disease and Felty's syndrome Excessive irradiation with the roentgen rays or radium may likewise be responsible for the *condition*

Purpura Secondary to Infections —It is known that *non thrombopenic purpura* is commonly associated with various types of infectious diseases but it should be recognized that occasionally a true thrombopenic purpura may be present in some patients due to this same cause Infection may provoke an attack of thrombopenic purpura especially in children The condition may appear either at the height of the disease or during convalescence Purpura of this type may accompany or follow measles chicken pox scarlet *fever or upper respiratory infections* It has also been observed occasionally in septicemia typhoid fever typhus miliary tuberculosis smallpox vaccinia and lupus erythematosus Thrombopenic purpura may be observed in patients with the blood picture of infectious mononucleosis according to Minot (*115*) Rosenthal (*116*) and Lloyd (*117*)

In all of these conditions it is unlikely that the diagnosis would be confused with the idiopathic variety of thrombocytopenic purpura because the fever and other features of the primary infection would be sufficient to aid in the differentiation It should be emphasized however that in some instances the evidences of the initial infection might be slight and *the purpura not appear until the convalescent period* It is wise therefore before concluding that a patient has idiopathic purpura to investigate carefully the possibility that it might be associated with mild infection in the convalescent state

Abnormal Bleeding Conditions in Association with Cancer —The association of secondary thrombopenic purpura with malignancy is well recognized This usually occurs in patients with neoplasms in which the metastases have diffuse infiltrating qualities and in those which *commonly involve the bone marrow the lungs and the ovaries* The stomach is most commonly the site of tumors which have characteristically this type of metastatic involvement A case illustrating the association of thrombopenic purpura secondary to carcinoma of the stomach is reported by Willis (*118*) who gives a review of 15 additional similar cases which have appeared in the literature According to this author's finding this occurs most frequently in young adults and the patients in addition to having a thrombopenia usually also have a moderately severe *anemia and immature red blood cells in the circulating* blood

In patients with cancer of the stomach the gastro intestinal symptoms may be so slight as to be overlooked and attention is focused on the

purpuric condition In such patients also the roentgenograms of the bone and lungs may fail to show evidences of the metastases Although thrombopenic purpura may be secondary to various types of cancer the possibility that it is in association with cancer of the stomach should always be considered in all patients in whom the etiology of the abnormal bleeding is obscure Furthermore, the development of such a type of purpura in persons known to have cancer should suggest strongly that metastases to the bone marrow had occurred Certainly it should be *remembered that the presence of purpura in patients other than children* suggests the possibility that it may be secondary to some malignant process Any malignant process which invades the bone marrow may reduce the number of megakaryocytes and thereby cause secondary thrombopenic purpura The purpura which occurs in patients with multiple myeloma is an example of this

Thrombopenic Purpura in Cirrhosis of the Liver —Attention is directed by Morlock and Hall (*119*) to the possibility that thrombopenia as well as hypoprothrombinemia is an important causative factor in some cases of hepatic disease associated with a hemorrhagic tendency This is supported by the observation that a definite thrombopenia was found by these observers in 17 5 per cent of 80 cases of hepatic cirrhosis It is of significance to note that although a definite hemorrhagic tendency was present in many of these cases regardless of the level of the blood platelets it was relatively twice as frequent when thrombopenia was associated The records of 50 cases of splenic anemia were also studied and it was noted that in 39 cases there was a tendency to bleed abnormally and in 48 8 per cent of these there was a definite thrombopenia In nine cases in which some form of bleeding occurred however the platelet count was normal *It is their opinion that the diminution of the blood platelets in cirrhosis of the liver is a significant finding and that such a change definitely increased the bleeding hazard* No explanation for the thrombopenia was discovered

Recently Woodward (*120*) reported the development of a thrombopenic purpura with a platelet count of 39 070 as a complication of acute catarrhal jaundice He assumed a diffuse derangement of the reticulo endothelial tissue in the spleen liver and lymph glands as the cause of this condition In his opinion this process was initiated by an apparently typical catarrhal jaundice

Allergic Thrombopenia —In recent years, there has been a considerable interest in the relationship of allergic states to the hemorrhagic diatheses Certainly there is clear evidence that some drugs probably on an allergic basis can account for a certain number of cases In others there is strongly suggestive evidence that various articles of diet may be responsible for the condition It is also possible that other allergins as yet unknown may play an important part in the production of abnormal

bleeding Whatever the role may be that allergy is found to play in the etiology of such disorders it should be emphasized that before splenectomy is done in patients who are supposedly suffering from the idiopathic form a careful investigation should be made in each instance to determine if a sensitivity to some allergen might account for the condition

The arguments in favor of an allergic etiology in this disease at least in some cases are 1 there may be a very suggestive history that following the ingestion of food or certain drugs the purpuric condition will invariably appear promptly 2 it has been demonstrated in some instances that the platelets of the circulating blood will decrease rapidly and purpuric spots will develop when the offending substance is administered to patients who are sensitive to it 3 the omission of certain supposedly offending foods from the diet or discontinuance of the drug which is thought to be responsible for the condition may be followed by periods of remission in the disease and 4 it can be demonstrated in some instances that the patient is sensitive to certain substances by cutaneous and intradermal tests or by the technic of passive transfer

On the other hand it must be remembered that idiopathic purpura is a disease in which the spontaneous course is one of remissions and exacerbations Hence the accurate evaluation of the relationship of any etiologic agent is difficult To be convincing it is necessary to demonstrate that in a large group of patients studied over a long period the manifestations of purpura always became apparent promptly after contact in one way or another with the suspicious allergen It is regrettable that most reports dealing with the subject have been based on observation of only a few cases and in some instances the blood studies have not been complete Furthermore all of the reasons given above for suspecting the relationship of allergy to the etiology of purpura must be considered as presumptive and circumstantial except the decrease in the blood platelets following the contact of the patient with the allergen If for example it can be shown repeatedly that following the ingestion of a drug or some article of diet there is *always* a prompt drop in the number of platelets the evidence is then conclusive To date however there are only isolated instances in which this has been demonstrated and even in some of these the platelet counts have not been convincingly low Also too much emphasis has been placed on relatively small changes in the platelet count which should not be considered as significant Furthermore it must be recognized that the error in the counting of blood platelets is one which is admittedly one of considerable extent Minor variations in the number of platelets in the circulating blood therefore cannot be accepted as proof that the decrease has occurred as a result of a specific sensitivity

Nevertheless additional studies concerning the relationship of allergy to the purpuric states should be encouraged as there can be no doubt but what certain drugs and foods and perhaps other unsuspected substances

may be responsible for the disease. Additional extended and carefully controlled studies are necessary, however, before any definitive statement can be made concerning this subject.

Thrombocytopenic Purpura Due to Various Drugs.—A considerable number of drugs have been reported as responsible for the production of thrombocytopenic purpura, especially arsenobenzol (*121, 122, 123, 124, 125, 126, 127*), the sulfonamides (*128, 129, 130, 131, 132, 133*) and sedormid (*134, 135, 136, 137, 138, 139*). According to Ackroyd (*140*) other substances occasionally causing this type of purpura are quinine (*141, 142*), quinidine (*143*), gold (*144, 145*), bismuth (*146*), iodine compounds (*147, 134*), chrysarobin (*148*), benzol (*149*), phenobarbitone (*150, 151*), alurate (allyl isopropyl barbituric acid) (*127*), nirvanol (*152*), sodium salicylate (*153*), leg stocking color preparations (*154*), thiourea (*155*), dinitrophenol (*156*) and colloidal silver (*157*).

A number of drugs which are of special interest in relation to thrombocytopenic purpura are discussed in detail in the pages which immediately follow.

Thrombopenic Purpura Due to Organic Arsenical Preparations.—Certain organic preparations of arsenic, mainly those employed in the treatment of syphilis, are known to be responsible for the development of a true thrombopenic purpura. By this is meant that the platelets alone of the circulating blood are affected and the resultant purpuric areas of the skin and mucous membranes are thus produced. It is also recognized that the arsphenamine group may cause the true picture of aplastic anemia in which purpuric manifestations occur.

It is interesting to note that arsphenamine, neoarsphenamine, sulfarsphenamine, silver arsphenamine and bismarsen (bismuth arsphenamine sulfonate) have all been observed to cause true thrombopenic purpura. It is known that mapharsen (the hemialcoholate of the meta-amino-parahydroxyphenyl arsine hydrochloride) has not caused attacks in some patients in whom thrombopenic purpura rapidly followed the injection of neoarsphenamine. According to Wintrobe (*158*), tryparsamide and inorganic arsenicals have not been reported as a cause of purpura, but he has observed three cases due to mapharsen.

The case of a 38 year old woman who developed thrombocytopenic purpura following the administration of neoarsphenamine and bismarsen is reported by Engelhardt and Bruno (*159*). After the patient had completely recovered, a test dose of 0.00005 gram of mapharsen was injected intravenously. *During the course of the injection, the patient complained of choking and a sense of constriction in the chest.* The platelet level had been between 325,000 and 360,000 per cubic millimeter before the test. *Twelve hours after the injection they fell to 135,000 per cubic millimeter.* At no time were petechiae or other hemorrhagic manifestations observed after the test dose had been given.

In a careful study by Falconer and Epstein (*160*), it was found that in a group of persons sensitive to neoarsphenamine or to bismarsen there was evidence of shock characterized by nausea, vomiting, chills, headache, hypotension and collapse which appeared immediately following the injection intravenously of these substances. Also within 15 minutes there occurred a drop in sensitive patients in the number of circulating blood platelets from which in some cases was as great as from a normal level to 50,000 per cubic millimeter. This low level was observed to continue, in some instances as long as 30 hours. Purpuric manifestations either generalized or localized to the arms, breasts and extremities appeared within a few hours to 24 hours following the injection. In five of the six cases studied by these observers there was purpura which was associated with a striking reduction in the circulating blood platelets. In one case there were large ecchymotic areas but no indication of a constitutional reaction or change in the level of the blood platelets which were constantly maintained within the limits of normal.

In discussing the mechanism of the production of the purpuric phenomenon Falconer and Epstein (*160*) state that it is difficult to believe that such an enormous number of platelets (a reduction for example in one patient of from 290,000 to 50,000 per cubic millimeter in 15 minutes) could be destroyed in such a short time. It is also significant that they observed the platelet count to rise from 80,000 to 170,000 per cubic millimeter within a brief interval following the injection of a 1 to 1000 solution of epinephrine. These observations led the observers to conclude that with the appearance of shock the capillary bed is dilated, thereby permitting a diffusion of blood into the skin which results in small hemorrhages constituting the purpuric spots. It is considered that patients showing this reaction have a prompt loss of circulatory tone, dilation of the capillary bed and a rapid loss of platelets from the circulation. The observation that a large number of platelets return to the general circulation following the injection of epinephrine and the rapid rise of the platelet count within 24 to 48 hours after the constitutional reaction has subsided are evidence *against* the assumption of widespread destruction of platelets.

Thrombopenic Purpura Due to Sedormid (allyl isoprophyacetyl carbamide).—The first report relating this hypnotic drug to thrombopenic purpura was by Dennig in 1933 (*134*) who observed a patient with purpura hemorrhagica which had followed the administration of a preparation containing iodine. After recovery from this there were two definite relapses each following the ingestion of one tablet of sedormid, a drug which the patient had not previously used. Following this Loewy (*161*) reported a similar occurrence. Hence the dangers of this drug were brought to the attention of the medical profession at large and additional reports rapidly accumulated.

According to Falconer and Schumacher (*162*) in a review of the literature up to November 1938 there had been reported 42 cases including their own A summary of their review of 36 cases shows that 24 women and 12 men usually of middle age or older, had been observed to have this condition They concluded that there seemed to be an increased susceptibility to the purpuric manifestations of sedormid among the older age groups in both sexes In those patients in whom platelet counts were made at the time of the purpuric manifestations the number was usually below 80 000 per cubic millimeter They administered two sedormid tablets to their patient after the evidences of purpura had disappeared and observed a fall in the blood platelets from 120,000 to 40 000 per cubic millimeter in about six hours This was associated with a shower of petechiae The formed elements of the blood other than the platelets showed very slight if any, alteration during the experiment Marrow obtained by sternal puncture before and after the administration of sedormid, showed no important changes except a rather striking decrease in number of platelets and the fact that they had a tendency to become larger (4 to 6 microns in diameter) and the evidence that the early granulocyte elements namely myeloblasts myelocytes and metamyelocytes are stimulated

Reports indicate that recovery is rapid as soon as the drug is discontinued In the majority of cases there is a complete disappearance of the purpura with cessation of the bleeding within three to 10 days According to the reports in the literature treatment including such measures as roentgen ray the administration of vitamin C blood transfusions and the giving of calcium and intramuscular injection of liver extract does not hasten the recovery of the patient

Apparently the drug can be taken daily in amounts of one to two tablets for weeks or even months without untoward effects and then the evidence of purpura developed Hence it can be concluded that the amount of the drug which is necessary to cause symptoms in patients varies widely Once a patient has become sensitized however the dosage which may produce the purpuric and hemorrhagic phenomenon is small usually two tablets

In the study of their patient Falconer and Schumacher (*162*) found no definite evidence that vitamin C either by oral or parenteral administration diminished the intensity of the purpuric lesions or hemorrhagic manifestations nor did it shorten the interval necessary for a recovery from these signs

The relatively large number of cases which have been reported following the use of this drug the consistent induction of a thrombopenia within six to eight hours after it is taken in a sensitized person and the disappearance of the purpura following its discontinuance indicate beyond the slightest question of a doubt that it may be responsible for

such a type of purpura The most satisfactory explanation of the reaction is that it is allergic in nature the sensitized state arising either as the result of continued administration or following an intermittent dosage

After a thorough study which merits careful perusal by anyone interested in the relation of this drug to thrombocytopenic purpura Ackroyd (139) came to the conclusion that two separate changes were responsible for the purpura in sedormid poisoning They were 1 a capillary defect and 2 a deficiency of circulating platelets which tends to increase the hemorrhagic tendency due to the capillary lesion This investigator demonstrated that the application of sedormid to the skin caused petechial hemorrhages in the area to which the drug was applied As there was no change in the platelet count following this it suggests strongly that the bleeding was due to increased capillary injury It was also shown however that platelets were agglutinated in vitro by sedormid and that the drug reduces clot retraction in the blood of patients who have recovered from sedormid purpura

Relation of Gold Therapy to Purpura —It occasionally happens that in the course of treatment with gold usually for rheumatoid arthritis a patient will develop purpura This may be of the thrombopenic or the non thrombopenic type This is a rare but serious complication of this form of therapy It is reported by Hartfall Garland and Goldie (163) that purpura developed in nine patients during the administration of 1415 courses of therapy which gives an incidence of 0 65 per cent In three cases it followed treatment with crisalbine two with solganal one with myocrisin and three with lopion Three of the cases terminated fatally two following the use of crisalbine and one after myocrisin The lowest number of platelets in seven of the cases were 25 000 35 000 50 000 151 000 (cases which recovered) and 38 000 90 000 and 285 000 (fatal cases) per cubic millimeter

It is the opinion of the authors cited based on information derived from capillary resistance tests on these patients with purpura as well as those without purpura that there is an element of capillary damage due to a peripheral toxic effect For example in 10 out of 14 non purpuric cases purpura has been induced by this test They consider therefore that two factors are involved in some of the cases of frank purpura One is probably a toxic effect on the hematopoietic tissues of the bone marrow and a consequent decrease in the circulating platelets thereby causing a thrombopenic purpura The other is possibly a peripheral effect on capillary endothelium which can be demonstrated by a positive capillary resistance test This is present in outspoken cases of purpura and also in some non purpuric toxic cases

Three of their cases who recovered were treated with large doses of ascorbic acid They considered a history of purpura as a definite contra indication to the use of gold as a therapeutic agent

Thrombopenic Purpura Following the Use of the Sulfonamide Drugs — Evidences of thrombopenic purpura have been reported following the administration of sulfanilamide (*164*) neoprontosil (*165*) sulfapyridine (*165*) sulfathiazole (*166*) and sulfadiazine (*167*) In each instance there was bleeding from the mucous membranes and petechiae of the skin along with a pronounced decrease or absence of platelets in the circulating blood

There does not seem to be any question therefore, but what many of these sulfonamide drugs are capable of producing true thrombopenic purpura but it must be an exceedingly rare complication considering the paucity of reports of such a nature, and the frequency with which this type of therapy is employed throughout the world

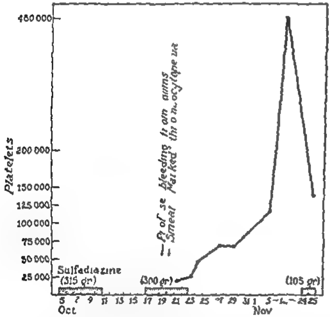

Fig 53 — *Changes in the blood platelets in a patient with abscesses of the lungs to whom sulfadiazine was given in three short courses after sulfathiazole had been previously adminis tered without ill effect for 6 days* Thrombocyto penic purpura developed shortly after the second course of sulfadiazine was instituted and thrombocy topenia occurred with a *platelet count of 138 000* per cubic millimeter but without clinical evidence of purpura immediately after the third course of sulfadiazine (Whitehouse and Watkins cour tesy *Staff Proceedings Mayo Clinic*)

It should be emphasized, however that the presence of purpura in a patient who is receiving any one of the sulfonamide preparations is in itself not positive proof that this condition is attributable to the medica tion In practically all cases these drugs are administered because the patient has an infection and purpura of this type is known at times to result from almost any type of infectious process Furthermore before assuming that the drug is responsible for the purpuric condition the case must fulfill the diagnostic criteria of acute thrombopenic purpura as previously stated *There must be 1 bleeding from the mucous* mem branes and into the subcutaneous tissues 2 a pronounced reduction in the number of platelets in the circulating blood 3 a normal coagulat ing time and prothrombin time 4 an absence of retraction of the blood clot 5 no other changes in the hemoglobin or red blood cells than can

be accounted for by hemorrhage 6 no unusual changes in the leukocytes and 7, an absence of splenomegaly and lymphadenopathy

It should be pointed out that the purpuric condition has resulted in some cases following the initial administration of the drug and in others after a short course followed by a cessation and then a resumption of the therapy In one patient it appeared after an initial dosage of only 5 5 grams of sulfathiazole (*166*) had been given over a period of three days In most instances the total amount of the drug taken did not exceed 20 to 30 grams and in some it was very much less

The most carefully reported study is that of Whitehouse and Watkins (*167*) who observed all of the classical manifestations of thrombopenic purpura in a 38 year old male who was treated for a lung abscess with sulfadiazine This patient had received 5 grams of sulfathiazole at home before admission From October 5 to October 10 he was given 21 grams of sulfadiazine without effect From October 17 to October 20 20 grams of the same drug was given On the second or third day of the second course of sulfadiazine bleeding from the gums appeared which later became profuse On the fifth day the blood platelets fell to 20 000 per cubic millimeter and the bleeding time was two hours Following the cessation of therapy and the administration of a blood transfusion the bleeding promptly ceased and the platelets rose to 480 000 per cubic millimeter Four and one half weeks later 7 grams of sulfadiazine was given over the course of two days The following day the platelets had dropped from a normal level to 138 000 and the medication was discontinued

Two cases are reported by Hurd and Jacox (*168*) in which one developed thrombocytopenic purpura following the administration of 14 grams of sulfathiazole and the other the same condition after having received sulfadiazine In the case of the first patient tests were done after he had completely recovered and it was found that a thrombocytopenia developed promptly after the administration of *both* sulfathiazole and sulfadiazine In view of the fact that these observers could demonstrate definite sensitivity to these drugs two months after the first reactions to sulfathiazole they concluded that extreme caution should be used with reference to their readministration following the development of thrombocytopenia even though previous observers (*169*) have not found that this was true Their second patient succumbed during the administration of the sulfadiazine Although death was attributed to the hemorrhagic state the authors could not dismiss the general toxicity of the pneumococcus pneumonia as the causative element that played a significant part in her death

There is ample evidence therefore to indicate that thrombopenic purpura is a possible but infrequent complication of sulfonamide therapy It is always a serious one for the mortality in the reported cases is 50

per cent Another point of interest and one that should be kept in mind by all who prescribe these preparations is that the condition usually follows the administration of relatively small amounts of any one of the sulfonamides In a series of eight cases summarized by Gorham and his associates (*165*) the amount of the drug administered varied from as little as 5 5 grams in three days to 48 grams over a period of 11 days Four of their patients received sulfapyridine two sulfanilamide, one sulfathiazole and one sulfadiazine

A point of practical importance is that the sooner the sulfonamides are stopped after the appearance of the purpura the better the prognosis for the recovery of the patient As the thrombopenia undoubtedly precedes the appearance of the purpuric manifestations, it would be advisable, when examining blood films from patients receiving sulfonamide therapy for the presence of granulocytopenia to make a careful study of the number of platelets which are present It has been suggested (*165*) that inasmuch as the chemical structure of sulfonamide benzol and aniline are similar, it is reasonable to assume that the production of the various blood dyscrasias by these substances involves the same fundamental mechanism

Quinine and Thrombopenic Purpura —A number of cases have been reported in which this variety of purpura has undoubtedly been due to a sensitivity to quinine salts Rosenthal (*116*) reports two cases due to quinine in which the condition simulated closely the idiopathic type One was in a newborn child Another is reported by Peshkin and Miller (*170*) in a 29 year old female mulatto who developed purpura with excessive bleeding from the skin and mucous membranes following the ingestion of quinine Apparently this patient was also sensitive to ergot as the same condition resulted when this drug was taken Skin tests demonstrated that she had a cutaneous sensitivity to quinine but not to ergot A 35 year old male was observed by Maritschek and Markowicz (*171*) who was said to have had quinine intoxication during treatment for malaria 15 years before coming under the care of these observers Following the ingestion of the drug there developed purpura and hemorrhages from the mucosae of the nose and mouth The sensitivity persisted as indicated by the appearance of thrombopenia a short time after the administration of 0 3 gram of quinine

I observed a 57 year old male on my wards who gave the history that 21 years previously he had hematuria and bleeding from the mouth and into the skin In the interval he had experienced a total of four such episodes It was ascertained that just prior to each attack quinine had been taken orally although until the relationship was pointed out to him this drug had not been associated in his mind with the periods of bleeding He was given 0 1 milligram of quinine intracutaneously as a test dose and the following observations made within two minutes a wide erythematous

area developed around the site of the injection but it was not purpuric Within five minutes the patient complained of nausea pallor developed and within 15 minutes the body temperature rose to 100 degrees (F) At the beginning of the test the platelet count of the peripheral blood was normal In about one half hour it began to fall and in one and one half hours the platelets had almost disappeared from the circulating blood At the end of three hours the platelet count was still low the tourniquet test was positive the clotting time 8½ minutes the bleeding time was 3½ minutes There was no clot retraction in 24 hours

Non Thrombopenic Purpura (Symptomatic Purpura)—Hemorrhagic States Due to Changes in the Capillary Walls—Undoubtedly this is the most common type of purpura as it may occur in any infectious disease and is regarded as the characteristic rash in some as typhus fever Rocky Mountain Spotted fever and cerebrospinal meningitis The damage to the capillary walls may occur in one of several ways In subacute bacterial endocarditis and other conditions the purpuric spots may result from bacterial emboli lodging in the minute capillaries This causes a direct necrotic action in the vessel wall and the escape of red blood cells into the surrounding tissues Not only does this occur in subacute bacterial endocarditis but it may also be the explanation of purpura in typhoid fever and the generalized septicemias A second method of injury to the capillary walls may be the direct action of toxins of any infection By this action there results a weakening and breaking of the endothelial lining of the capillaries

In the purpura of scarlet fever Fox and Enzer (172) concluded that sensitization of the capillary endothelium appears to afford a reasonable explanation for the purpura as it is known that the scarlet fever toxin causes swelling of these cells in areas of erythema Likewise these same authors consider that hematuria in scarlet fever in the absence of other evidence of nephritis is perhaps the result of the effect of the scarlet fever toxin on the glomular endothelium and hence the condition should be regarded as renal purpura

There is some confusion in the classification of the purpuras because the same infection may cause purpura due to capillary injury in some and purpura in others due to a decrease in the number of circulating platelets In still other cases it seems reasonable to suppose the purpuric manifestations may be due to both mechanisms It has been suggested by Davidson and his associates (173) that the problem is intimately connected with two issues (1) the intensity and duration of the intoxications and (2) the variability of the reaction of tissues in different individuals It is their belief that possibly long continued infection or intoxication is more likely to cause bone marrow aplasia and thrombocytopenia than a sudden short and intense infection or toxemia which may produce capillary damage

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Schonlein Henoch s Purpura—The relationship of the sensitivity or allergy to drugs articles of diet and the products of bacteria all of which may be responsible for purpuric manifestations have been previously discussed Since the knowledge in this field is incomplete any grouping or classification in which an allergic basis is used is subject to revision in accordance with the future development of knowledge in this field In the classification which I have presented purpura is considered to have an allergic basis and to produce characteristic lesions by the following mechanisms 1 the reduction of platelets (allergic thrombopenic purpura) 2 by changes produced in the capillary walls (nonthrombocytopenic purpura) and 3 the type of purpura which is considered in this section namely the Schonlein Henoch variety This latter condition is considered to be an allergic non thrombopenic purpura associated with the common evidences of allergy such as erythema urticaria and effusions of serum into the subcutaneous and submucous tissues of a viscus Such changes are not due to hematopoietic disturbances but are concerned with a generalized increased permeability of the capillary endothelium as an expression of the allergic state which permits the passage of plasma and red blood cells Such a change therefore serves as a basis for the visceral symptoms

Etiology—The cause of this variety of purpura is now considered to be a sensitivity to various allergens It has been demonstrated that the following may be responsible for the condition bacterial (the streptococcus tubercle bacillus) milk egg wheat potato chicken pork beans coffee strawberries plums and peanuts It has suggested (*175*) that cold might produce the condition in rare instances

Pathology—The visceral lesions are of two types namely 1 mechanical due to exudate on the walls of the stomach or intestine and the effusion of blood into the substance of an organ or on a mucous surface and 2 inflammatory like reactions such as nephritis and less often endocarditis pleurisy pericarditis pneumonia and peritonitis

That such cases might have an allergic basis was emphasized by Osler in 1914 (*176*) who suggested that Before long the anaphylactic key will unlock the mysteries of these cases In 1927 and also in 1928 the allergic nature of these symptoms was pointed out by Alexander and Eyermann (*177*) They based their conclusions on a history of the associated allergic manifestations the presence of positive skin reactions the production of symptoms after the deliberate feeding of suspected allergens and finally the subsidence of the symptoms after these articles were rigidly excluded from the patient s diet

The characteristic symptoms such as colicky abdominal pain and tenderness nausea and vomiting and occasionally diarrhea are produced by edema and spasm of smooth muscle of the intestines The purpura and edema arise as a result of the passage of plasma and red blood cells

The characteristic rash in cerebrospinal meningitis in typhus fever and in Rocky Mountain Spotted fever is purpuric in type Also in severe cases of measles smallpox and scarlet fever, the rash may become hemorrhagic in nature In all of these conditions it is thought that the purpura is due to capillary injury On the other hand it must be admitted that careful blood studies dealing with the blood platelets, and the amount of prothrombin and fibrinogen in the circulating blood are lacking in these conditions It is possible that future studies will show that such changes may be of importance in relation to the hemorrhagic features in these infections

Various Drugs as a Cause of Purpura Due to Increased Permeability of Capillary Walls—Certain drugs may cause purpura apparently by producing a defect in the capillary walls In such a condition there may be no reduction in the number of circulating platelets Those which have been reported as responsible for such a change are atropin bismuth belladonna chloral hydrate copaiba mercury merbaphen phenacetin and the salicylates When such an alteration occurs which is rare it is assumed that the individual is sensitive to the preparation It is also known that the purpura which occurs in poisoning with snake venom is due, in part at least to capillary wall injury

The Purpura Associated with Nephritis—There are three possible explanations of the purpuric conditions observed in some cases of nephritis It may be due to 1 retention of nitrogenous products acting in some unknown manner as suggested by Davidson and his associates (*173*) In such cases the purpuric condition usually occurs in the advanced stages of the disease and the presence of purpura therefore heralds the approaching end 2 In cases of acute nephritis it is reasonable to assume that the purpura can be attributed to injury of the capillary endothelium due to its susceptibility to damage by toxic substances possibly of streptococcic origin 3 In patients in which the condition is neither acute nor advanced to the stage in which there is retention of nitrogenous products it is thought by some that an associated hypertension may be the basis for the bleeding state This is based on the findings of Levrat and Ballivet (*174*) who found that many persons with hypertension gave a positive tourniquet test and hence they concluded that purpura in such patients is mechanical that is due to an increased arterial pressure which is transmitted to the capillaries or is based on increased capillary fragility Davidson and his associates (*173*) do not agree with this view as he has stated that his studies lead him to conclude that there is no relationship between arterial hypertension increased venous pressure kidney disease and the occurrence of purpura It is difficult to say how important the mechanical factor or fragility of the capillaries is in relation to purpura which occurs in hypertension but it must be accepted that the tourniquet test is positive in a certain number of patients with this condition

and noticed a persistent hematuria A severe anemia was present as shown by a hemoglobin of 44 per cent and a red blood cell count of 2 6 millions per cubic millimeter Clotting time was eight minutes and bleeding time 13 minutes The tourniquet test was negative The blood platelets numbered 285 000 per cubic millimeter The bone marrow obtained by sternal aspiration showed no significant changes Sensitization studies and an elimination diet failed to establish definitely an allergic basis for the purpura but apples pears and eggs caused upper abdominal discomfort with nausea The urine contained large quantities of albumin many red blood cells and cellular and granular casts The non protein nitrogen of the blood rose to 145 milligrams per 100 cc and the patient died with the clinical manifestations of uraemia Necropsy showed far advanced glomulotubular nephritis and petechial hemorrhages in the bronchi lungs and colon

Renal Complications —The involvement of the kidney in purpuras of this type is one of the most serious complications which is known to occur and one which may lead to a fatal termination as the result of uraemia The nature of the kidney change is not well understood Osler (*176*) reports one case in which the kidneys were grossly enlarged and had changes regarded as glomerular nephritis in which with great proliferation of the epithelium there was also a new growth of connective tissue within the capsuls

According to Osler (*176*) there are several clinical features of this type of nephritis which are of interest They are as follows first long after all cutaneous lesions have disappeared the urine may contain blood second the albuminuria is usually pronounced third tube casts may be scant or absent and fourth the albuminuria may persist for months after the patient has recovered his usual health

Schonlein s Purpura —This condition is characterized by joint pains in association with urticarial and purpuric skin lesions The condition is most commonly observed in young adults and as the joint involvement is usually migratory it may simulate the clinical picture of acute rheumatic fever It is not however amenable to treatment with the salicylates The joint condition is usually ascribed to a periarticular effusion It would seem to me that it might be on the same basis as the joint symptoms which are observed in serum sickness except that the latter are greatly relieved by salicylate therapy

Laboratory Findings —It is not common to have an anemia in this type of purpura but there may be sufficient bleeding from either the bowel the kidney or both to produce a lowering of the hemoglobin to 50 per cent and the red blood cell count to 2 5 millions per cubic millimeter or less The white blood cell count is usually normal unless there is a considerable amount of acute hemorrhage A neutrophilic leukocytosis is sometimes present and there may be an increase in the number of eosino

through the walls of the capillaries which have become more permeable The tenderness in the region of the joints which is sometimes an outstanding symptom is associated with a periarticular effusion Acute nephritis may occur which is usually of the hemorrhagic type in some instances it may progress to chronic nephritis and death may occur from uraemia

In summary it may be said that in this condition which is now thought to be on an allergic basis there may occur as the result of increased permeability of the capillary walls the passage of plasma and red blood cells into the tissues of the intestinal tract, the skin the brain the eye and other parts of the body In some instances there may be an associated acute nephritis which may progress to the chronic variety As the fundamental pathological lesions may involve almost any tissue in the body it is easy to understand why the clinical picture may be so diverse

Clinical Manifestations —According to Osler (*176*) there are two outstanding clinical features first the recurrence of attacks at long or short intervals over periods ranging from a few months to many years and secondly, the morphological inconstancy of the skin lesions There may be for example angioneurotic edema purpura and necrotic sloughs in a single attack Osler in his report of 1914 recites the case histories of a number of patients in which the following manifestations of the disease are present 1 hemiplegia in which the attack is transient and those in which the paralysis is due to a gross hemorrhage 2 ocular lesions with hemorrhage into the eyeball 3 gastro intestinal symptoms Henoch s purpura and 4 renal complications

Henoch s Purpura —This is the name applied to the group of patients who have attacks of colicky abdominal pain with nausea and vomiting and sometimes diarrhea with the passage of blood in the stools These symptoms arise from a serohemorrhagic effusion into the walls of the intestine which is a local manifestation of allergy The attacks may be present with urticaria and purpura or they may occur without them If the abdominal symptoms are present without the skin lesions the condition may simulate one requiring abdominal surgery and lead to a needless surgical operation

A typical case of Henoch s purpura with death resulting from uraemia was seen by me in 1941 The patient was a male of 21 years who developed attacks of sharp cramping abdominal pain at the age of 18 years These episodes were accompanied by nausea and the severe ones by vomiting They usually persisted for three or four hours and occurred every three or four months In the interim he felt perfectly well Four months before admission he experienced an especially severe attack which differed from the previous ones in two important features namely he passed pure blood from the bowel and purpuric areas appeared over the extremities Shortly after this he developed swelling of the face

Clinical Picture.—Ninety per cent of the cases occur in children who are from six months to nine years of age about 70 per cent of the patients are said to be under two years of age The earliest clinical manifestations are malaise anorexia and slight elevation of body temperature There is commonly vomiting but it is not a persistent feature Abdominal pain and diarrhea are sometimes present. Within eight to 12 hours a characteristic cyanosis develops and this is soon followed by petechial mottling of any part of the body Weak and irregular heart action and peripheral collapse are likely to become apparent as the condition of the patient becomes more critical Cyanosis and purpura are present in practically all cases The course is universally rapidly fatal almost without exception

The pathological findings are the petechiae and purpuric ecchymoses on the skin and mucous membranes and the massive adrenal hemorrhages Microscopically the cutaneous hemorrhages are seen to be due to direct involvement of the capillaries and the arterioles The blood platelets are said to be normal in number In the opinion of Lindsay and his associates (*181*) the Neisseria meningitis is responsible for the majority of cases and Hemophilus influenzae may account for the greater proportion of the remainder

Treatment.—Although practically every case is fatal therapeutic measures should be instituted to 1 combat the infection 2 cope with the suprarenal damage and 3 support the patient It will be of interest to learn the effects of the sulfonamide drugs and penicillin in the treatment of this condition If it were possible to make the diagnosis early in the course of the disease before massive adrenal damage is done these should be of therapeutic value

Scurvy.—This condition is a nutritional disorder due to a deficiency of vitamin C (ascorbic acid) which in its advanced state is accompanied by a hemorrhagic tendency as characterized by bleeding gums subperiosteal hemorrhages ecchymoses petechial hemorrhages but most typical of all small hemorrhages about the hair follicles (peri follicular hemorrhages) They are most frequently encountered over the lower extremities or where there is pressure on the skin

The abnormal bleeding tendency is dependent upon an increased capillary permeability as can be demonstrated in both active and latent scurvy by means of the tourniquet test or by the application of a suction apparatus to the skin This change in the capillaries is thought to be due to a defect in the intercellular substances which is normally present in connective tissue bone and teeth Morphologic alterations however have not been demonstrated in the capillaries It is thought that future studies may show that the weakness is in the cement substance which fuses the epithelium of the capillaries together or in the connective tissues and collagen fibers which ensheath the endothelium

Verification of a clinical diagnosis of scurvy as the basis for a hemorrhagic tendency may be made by the estimation of the blood ascorbic

phils Changes are not observed in the bleeding time clotting time, clot retraction or the number of platelets Blood may be present in the urine and stools A heavy albuminuria is usually present in those patients who have a definite renal involvement

Diagnosis —A history of recurrent attacks of pain in the abdomen or about the joints in association with purpura and other allergic manifestations at once suggests the possibility of this type of purpura In some instances there may be signs of renal involvement either in the form of hematuria with a normal function or there may be an indication of more pronounced involvement as shown by a decrease in renal function A history of allergy which has shown itself in one way or another is helpful in the diagnosis as are the skin tests, and the recognition that a definite relationship exists between the ingestion of certain articles of diet and the production of the characteristic symptoms Even more convincing evidence may be obtained by the administration of the suspected foods to determine if they produce the characteristic symptoms and signs One should be cautious before making a diagnosis of purpura of the Henoch Schonlein group to eliminate carefully all other types of non thrombopenic purpura

Treatment —The treatment consists in the detection of the suspected foods to which the patient is allergic and eliminating them from the diet A list of those foods which have been found to be the cause of the condition is given under the section dealing with etiology of this disorder Doubtless there are many more which have not been detected The most effective way in which this can be accomplished is to place the patient on an elimination diet and gradually add the foods one at a time which are suspected from the history of being responsible for the condition In some cases but by no means all it is possible to establish a definite relationship between the ingestion of food and the production of symptoms

Additional Types of Allergy Due to Food and Drug Sensitivity —It does not seem possible to regard as a separate group the different purpuras not accompanied by other allergic manifestations which appear to be due to sensitivity toward various types of food and drugs In other words although there are instances of non thrombopenic purpura, which are apparently allergic manifestations no other evidences of allergy may be determined Such cases undoubtedly do occur but more information concerning these is desirable For the present however they should be included in the anaphylactoid group along with the Henoch Schonlein variety

The Waterhouse Friederichsen Syndrome —The earliest report of this disorder was by Voelcker (*178*) in 1894 who described it as a fulminating purpura associated with bilateral adrenal hemorrhage The designation "Waterhouse Friderichsen syndrome" is derived from the names of the observers who studied the condition and suggested a possible bacterial etiology (*179 180*)

by the use of it in some of the non scorbutic hemorrhagic diseases. Subsequently he and his collaborators isolated a flavin which they designated as vitamin P. This substance they considered to be responsible for the effect. The name was applied because the material was isolated from paprika and because it was thought to influence the permeability of the capillaries.

At the present time it is not possible to say that there is clinical evidence in support of this view and further studies are necessary before the therapeutic value can be established. Rappaport (*184*) treated 12 children who were found to have an increased capillary permeability with vitamin P (calcium eriodictate 100 to 150 milligrams daily) at intervals over a period of six months. He observed that the capillary fragility became normal following the administration of this vitamin. It was his conclusion that vitamin P apparently plays an important role in the mechanism of the permeability of the capillary wall. Scarborough (*185*) in summarizing his views concerning vitamin P states that in his opinion the vitamin does exist but that it cannot at present be regarded as a potent therapeutic agent in any one of the hemorrhagic diseases. He cautions further that it is illogical to make statements about the ineffectiveness or otherwise of vitamin P in the treatment of the various forms of purpura until (a) it is known what vitamin P is (b) until suitable preparations are available for administration and (c) until their effects have been tested on suitable cases.

More recent investigations have shown that vitamin P which is also called citrin is a mixture of two flavones in the form of their glucosides. Another flavone derivative resembling vitamin P in its action is *rutin* present in tobacco leaves and buckwheat.

Rutin according to Rodrigues and Root (*186*) is believed to influence capillary fragility. They describe the material as a rhamaglucoside a derivative of flavanol. It is a tasteless yellow non toxic powder consisting of needle like crystals. According to these authors both rutin and hesperidin are constituents of plants such as garden rue and tobacco and are similar in structure. The chemistry of both rutin and hesperidin is described in detail by Couch Naghski and Krewson (*187*).

The studies of Rodrigues and Root are of interest because they found that when rutin was given in doses of 20 milligrams three times daily and the dose raised 40 or 60 milligrams three times daily in some cases an increased capillary fragility in patients with diabetes and retinitis can be brought to normal although in no case was the associated diabetic retinitis improved. On the other hand the results of studies by Barnes (*188*) are not in accord with those reported by Rodrigues and Root. This observer concludes that when the drug was given even in daily doses of 300 milligrams for as long periods as 18 to 30 months it did not appear to have an effect on improving the capillary fragility or the

acid which is usually exceedingly low or entirely absent Of further diagnostic aid is the application of the therapeutic test by means of the administration of 250 milligrams of ascorbic acid or 480 cc of orange juice daily With this amount of antiscorbutic material the manifestations of the disease should be improved dramatically in from two to seven days

Scurvy is not a common cause for a hemorrhagic tendency in the United States but it should always be kept in mind in the presence of abnormal bleeding which cannot be explained by any cause such as thrombopenic purpura hemophilia or other disturbance in the bleeding mechanism In the few adults I have seen with the condition they have either been of the freak variety who had curious ideas about their own dietary intake and existed for long periods of time on one which was deficient in vitamin C or had been on an improper diet for the treatment of peptic ulcer The latter had usually been one which they had devised It should be remembered that Field and his associates (*182*) have shown that the administration of a large amount of alkalies interferes to a certain extent with the absorption of vitamin C and hence in peptic ulcer, this with a low intake of the vitamin might account for varying degrees of deficiency in these patients It has not been my experience however, that frank evidences of scurvy have occurred in these patients who have partaken of any of the standard recognized methods of treatment for peptic ulcer

The recognition that scurvy is the explanation of a hemorrhagic state is not difficult if the condition is kept in mind The presence of peri follicular hemorrhages other petechiae or ecchymoses and bleeding gums in a patient who is partaking of a diet which is obviously deficient in vitamin C at once suggests the diagnosis With this there is a positive tourniquet test and no indication of any abnormality in the bleeding or coagulating time retractility of the clot or changes in the number of platelets A study of the blood ascorbic acid and the response to anti scorbic therapy are confirmatory tests

Although it is not rare to have an associated anemia in patients with scurvy it is not clear that it is directly due to a deficiency of vitamin C It may possibly be attributable to the excessive bleeding from the gums or gastro intestinal tract or what is more likely it may be associated with some other deficiency such as one of iron or protein When present the anemia is usually normocytic but occasionally it may be macrocytic It is unlikely that vitamin C is directly related to the formation of blood and hence it probably does not play a direct role in the production of an anemia

The Relation of Vitamin P to Capillary Permeability —In 1936 Armentano and his associates (*183*) in observing the effects of impure preparations of vitamin C believed that they obtained a therapeutic effect

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Scurvy is not a common cause for a hemorrhagic tendency in the United States but *it should always be kept in mind in the presence of* abnormal bleeding which cannot be explained by any cause such as thrombopenic purpura, hemophilia or other disturbance in the bleeding mechanism. *In the few adults I have seen with the condition they have* either been of the "freak" variety who had curious ideas about their own dietary intake and existed for long periods of time on one which was deficient in vitamin C or had been on an improper diet for the treatment of peptic ulcer. The latter had usually been one which they had devised. *It should be remembered that Field and his associates (182) have shown* that the administration of a large amount of alkalies interferes to a certain extent with the absorption of vitamin C and hence in peptic ulcer this with a low intake of the vitamin might account for varying degrees of deficiency in these patients. It has not been my experience, however, that frank evidences of scurvy have occurred in these patients who have partaken of any of the standard recognized methods of treatment for peptic ulcer.

The recognition that scurvy is the explanation of a hemorrhagic state is not difficult if the condition is kept in mind. The presence of perifollicular hemorrhages, other petechiae or ecchymoses and bleeding gums in a patient who is partaking of a diet which is obviously deficient in vitamin C at once suggests the diagnosis. With this there is a positive tourniquet test and no indication of any abnormality in the bleeding or coagulating time, retractility of the clot or changes in the number of platelets. A study of the blood ascorbic acid and the response to antiscorbic therapy are confirmatory tests.

Although it is not rare to have an associated anemia in patients with scurvy, it is not clear that it is directly due to a deficiency of vitamin C. *It may possibly be attributable to the excessive bleeding from the* gums or gastro-intestinal tract or what is more likely it may be associated with some other deficiency such as one of iron or protein. When present the anemia is usually normocytic but *occasionally it may be* macrocytic. It is unlikely that vitamin C is directly related to the formation of blood and hence it probably does not play a direct role in the production of an anemia.

The Relation of Vitamin P to Capillary Permeability.—In 1936 Armentano and his associates (183) in observing the effects of impure preparations of vitamin C believed that they obtained a therapeutic effect

pseudohemophilia because the typical features of that disorder such as severe bruising from slight trauma recurrent visceral hemorrhages and a prolonged bleeding time are absent He regards the condition as the most benign of the hereditary hemorrhagic diatheses At the other extreme is hemophilia and between them comes pseudohemophilia. The patients do not usually seek medical advice for this condition and they are not often aware that other relatives are affected

HEREDITARY HEMORRHAGIC TELANGIECTASIA

Synonyms —Hereditary epistaxis hereditary angiomata familial telangiectasia

Definition —This condition is a hereditary vascular anomaly characterized by hemorrhage from the capillaries and venules of the skin and mucous membranes which often gives rise to a hypochromic anemia

History —Hereditary telangiectasia was first described by Sutton (*193*) A year later Babington (*194*) reported the closely allied condition of hereditary epistaxis in five generations of one family It is likely that Legg (*195*) gave the initial comprehensive description of the disease In 1887 Chiari (*196*) reported the presence of epistaxis and multiple telangiectases of the skin and mucous membranes in four generations Rendu (*197*) later published a very excellent account of the condition in 1896 as did Osler (*198*) in 1901 and Weber (*199*) in 1907 These three early descriptions of the condition led to the designation "Rendu Osler Weber disease"

Etiology and Pathology —The bleeding arises from small telangiectatic lesions which may be located on the mucous membranes of the nose and mouth the skin of the face or elsewhere on the body the tongue the stomach and the intestinal tract They are also said to occur in the brain and the mucous membranes of the gastro-intestinal tract (*200*)

The bleeding results because as Steiner (*201*) states the capillaries of the small veins are dilated and their walls are composed only of a single layer of endothelial cells without the additional presence of elastic or muscle fibers As a result they are weakened and therefore subject to bleeding either spontaneously or from slight trauma

There is abundant evidence to indicate that the condition is on an hereditary basis as in a majority of cases there is another person in the family and sometimes a considerable number of blood relatives who are afflicted with the disease In my own group of seven patients four stated that at least one close relative was affected Of the remaining three patients the family history was not obtained in one and in the other two there were no similar cases in the family Hence although a family history is of importance from the standpoint of diagnosis the absence of another case in the blood relatives does not cast serious doubt on the diagnosis in any patient under consideration from this standpoint

diabetic retinopathy *It is apparent from these discordant results by reliable observers that any conclusions concerning the efficacy of rutin in the treatment of conditions due to an increased capillary fragility must await further evaluation*

Capillary Fragility in the Newborn —An observation of importance relating to bleeding in the first week of life has been made by Moloney (*189*) who studied the occurrence of abnormal capillary fragility in the newborn He found by using the resistometer of Dalldorf (*190*) which applies suction to the skin that 60 per cent of 55 newborn infants showed more or less abnormal capillary fragility Tests were carried out within the first 24 hours of life and then every day, until the fourth day If negative no further determinations were made otherwise tests were repeated until the eighth day It was observed that the decreased capillary resistance disappeared as the infants became older

After considering the various causes which might be responsible for the change in the capillaries in the first few days of life Moloney was inclined to attribute them to the combined effects of labor analgesia and anaesthesia which might result in anoxia in the infant In this connection it is interesting to note that where labor averaged 14 hours capillary fragility in infants was severe and very severe whereas when the capillary fragility was moderate slight or negative the average duration was approximately five hours He concludes in his preliminary report that the finding of abnormally low capillary resistance in a number of infants, during the period when hypoprothrombinemia and hemorrhagic disorders occur most frequently may have a relationship to abnormal bleeding in the newborn

Hereditary Familial Purpura Simplex —The importance of this condition has been emphasized by Davis (*191 192*) It is a familial hereditary disorder characterized by spontaneous ecchymoses seen mostly but not exclusively in females and occurring commonly at the climacteric Davis has reported the condition in 27 families comprising 88 members of whom 84 were females with spontaneous skin ecchymoses In nine of the 27 families purpura occurred in one generation only in 12 in two generations in five in three generations and in one family in four generations Of the 88 cases 79 had purpura simplex six purpura of the Schonlein Henoch type two bruised on trivial traumata and one a boy had pseudo hemophilia

These patients usually do not consult a physician as their complaints are minor ones in most instances Occasionally there is a history of epistaxis or menorrhagia The bleeding time clotting time and platelet counts are normal although the capillary resistance test is often positive Hemorrhages into the viscera do not occur Thus type of purpura is not infrequently associated with rheumatic fever and rheumatoid arthritis

According to Davis (*191 192*) this condition is clearly not the hereditary hemorrhagic thrombasthenia of Glanzmann subsequently called

by Alban (*202*) in which the disease was found in 19 of 102 members in six generations and he predicted that even more cases will be added as the younger members reach the age at which the disease usually manifests itself. The literature from 1933 to 1944 has been reviewed by Stock (*203*) who adds the third recorded instance in the last 11 years in which the disease can be traced through six generations in one family.

The disorder is transmitted as a simple dominant characteristic. Both sexes are equally affected and may transmit the disease. Although from a theoretical standpoint the disease should appear in each generation, Fitz Hugh (*204*) has called attention to the fact that it may be atavistic and skip a generation. This may be because the condition is sometimes mild and hence in some cases may not have an important tendency to bleed. For this reason it may be overlooked.

The pathological changes associated with the disease have been reviewed by Schuster (*205*). This observer reported telangiectasia to be present in the skin, nose, mouth, pharynx, larynx, stomach and duodenum. He also found in a typical case dilated and distorted fibrotic veins in the upper lobe of one lung and beneath the surface of the liver capsule. Of special interest were small multiple aneurysms of the splenic artery. It is reported by Rundles (*206*) that the roentgen appearance and physical findings in a case observed by him in a 56 year old male factory worker strongly suggested an arterial dilatation of the pulmonary artery comparable to the splenic aneurysms described by Schuster, although the former suggests that the condition might be attributed to a vascular tumor with arteriovenous communication. The patient observed by Rundles had evidence of hemorrhagic telangiectasia with repeated epistaxes from the age of 14 years and in later life gastro intestinal hemorrhage was severe enough to produce an incapacitating anemia. Multiple gastric telangiectases were seen by gastroscopic examination. The aneurysm of the pulmonary artery did not increase appreciably during the period of seven years observation.

Symptoms and Signs.—The telangiectases seen in this disease are of three types: the pinpoint lesion which is most commonly present on the skin of the hands and face and which is relatively inconspicuous, the spider angiomas which are similar to those observed in some cases of cirrhosis of the liver, and the nodular type which sometimes originates in the center of a spider angioma and forms a solid vascular tumor about the size of a split pea. The most common sites of the lesions are the cheeks, the lips, the tongue and the tips of the fingers, although they may occur almost anywhere on the skin and mucous membranes of the body.

The disease may be present in childhood but the characteristic blood vessel changes are often inconspicuous at that time of life. They do not attain their full development until about the age of 35 years.

There may be recurrent epistaxis in childhood but usually the condition is not then responsible for symptoms. As the patient grows older

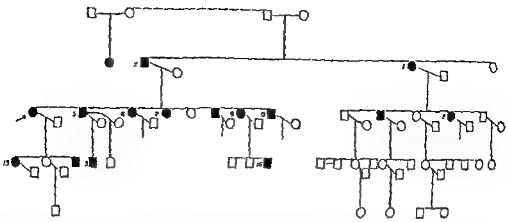

Fig 54 —The pedigree of a family with hereditary hemorrhagic telangiectasia Males are indicated by squares females by circles and affected individuals in black with reference numbers Apparently the correct diagnosis had not been made previously in any given patient (1) 64 year old woman An enlarged spleen had been removed for treatment of anemia (2) Male who lived to the age of 85 years He had profuse nosebleeds from early youth possibly hemoptyses and visible telangiectasia over the face ears tongue and fingers (3) Female who lived to the age of 84 years She had many visible telangiectasia frequent nosebleeds and a chronic anemia (4) 66 year old woman From girlhood she had frequent nosebleeds and conspicuous telangiectasia over the face ears tongue and fingers A severe anemia splenomegaly hepatomegaly and an enlarged heart erroneously thought to be due a valvular heart disease had been present for 30 years (5) 65 year old male Profuse nosebleeds conspicuous telangiectasia pallor and anemia were present throughout adult life (6) Female who died at 35 years of age in childbirth She had had profuse nosebleeds visible telangiectasia with a severe anemia for many years (7) Female age 61 years She had profuse epistaxes and visible telangiectasia appearing early in life (8) 60 year old male Spontaneous nosebleeds were frequent but not profuse (9) 56 year old woman Profuse nosebleeds began in her teens and visible telangiectasia were present Weakness pallor and severe anemia were chronic during her adult life (10) Male who died at the age of 44 years of intracranial disease following nasal cautery He had had profuse nosebleeds and projectile hemorrhages from a lingual telangiectasia (11) 56 year old male Profuse nosebleeds were chronic and there was no response to local treatment He was always pale and anemic (12) Female who died at the age of 33 years of a cerebral hemorrhage She had had profuse nosebleeds all of her adult life (13) Female age 33 years She had experienced occasional spontaneous epistaxes and examination showed scattered telangiectasia on the nasal septum face ears and tongue (14) Male killed in warfare at the age of 21 years He had had an increasing number of spontaneous nosebleeds (15) Male accidentally asphyxiated at the age of 17 years He had had frequent spontaneous and nocturnal nosebleeds (16) 20 year old male He has had increased frequency of nosebleeds but no evident telangiectasia

Many of the remaining members of this family are still too young to exhibit severe symptoms even if they were affected (I am indebted to Dr R Wayne Rundles for the permission to use these data which he collected while an instructor in Internal Medicine University of Michigan)

In one of my patients the disease occurred in her mother maternal grandfather and uncle one of her own brothers and one of the brother s sons A fatal hemorrhage had occurred in mother brother A family record is reported by Steiner (201) in which the condition occurred in five persons of five generations in a family with 21 members A family tree is recorded

by Alban (202) in which the disease was found in 19 of 102 members in six generations and he predicted that even more cases will be added as the younger members reach the age at which the disease usually manifests itself The literature from 1933 to 1944 has been reviewed by Stock (203) who adds the third recorded instance in the last 11 years in which the disease can be traced through six generations in one family

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bleeding from the nose and the gastro intestinal tract may result in a severe hypochromic microcytic anemia with the production of symptoms characteristic of an anemia namely, pallor weakness dyspnea and palpitation Lesions in the stomach may cause hematemesis and the characteristic telangiectases may be observed through the gastroscope (207) Libman and Ottenberg (208) have reported a family of seven who suffered from recurrent attacks of hemoptysis in which they concluded that the general characteristics of the condition resembled chronic hereditary telangiectasia

Epistaxis is the most common form of bleeding and it is most frequently the reason why the patient seeks medical advice The bleeding varies greatly in frequency and severity for it may be only oozing which recurs at frequent intervals or persists without interruption for several days In some instances however, the hemorrhages may be profuse Sometimes they are initiated by sneezing or coughing or some other strain but they may arise spontaneously while the patient is at complete rest These hemorrhages may recur at intervals of several weeks or be repeated four or five times daily It is not unusual for the patient to lose several hundred cubic centimeters of blood during a single episode of bleeding

In some patients there may be a palpable spleen and liver which in my experience may arise in association with chronic hypochromic anemia of long duration due to hemorrhage

Blood Examination—The blood in this condition usually shows a hypochromic microcytic anemia which is the result of chronic hemorrhage This is indicated by a moderate reduction in the red blood cells usually in the vicinity of 2 5 to 3 5 million per cubic millimeter and a hemoglobin which varies between 25 and 50 per cent of normal The color index is ordinarily between 0 5 and 0 7 If there has been recent acute hemorrhage there may be an increase in the polymorphonuclear cells of the circulating blood and the blood platelets For a short interval following the sudden loss of blood the red blood cells may be macrocytic or normocytic rather than microcytic During the period of active blood regeneration there may be an increase in the number of reticulocytes in the circulating blood and nucleated red blood cells may be present Otherwise the blood shows no abnormalities The bleeding time and clotting times are within normal limits as is the prothrombin time There is never a reduction in the blood platelets

Diagnosis—The diagnosis of the condition is simple if the disease is kept in mind If the patient is observed to have telangiectatic lesions especially on the cheeks tongue and finger tips and is suffering from the usual symptoms of a hypochromic anemia the diagnosis is immediately suggested If there is a history of one or more other cases in the family it is at once established One should not hesitate to make the diagnosis in the absence of a positive family history because as previously stated,

some cases may be so mild that they do not attract notice and as reported by Fitz Hugh (*204*) the condition may skip one generation

It is amazing how often the diagnosis is overlooked The condition was not recognized in the first case which I observed until some months later when I saw his sister who was admitted to the hospital with the same condition Another patient was incapacitated with the disease for the greater part of eight years and was first regarded as having simple anemia The diagnosis was then changed to pernicious anemia and finally to secondary anemia of unknown etiology before the correct diagnosis was determined Another patient was treated for a period of one year for a peptic ulcer because there was bleeding from the gastro intestinal tract Ventriculin and liver extract had been given to another patient for four years before the true nature of his malady was established Banti s disease was considered in another patient because there was a severe anemia with a low color index a leukopenia and a palpable spleen Splenectomy was considered but fortunately the true condition was discovered in time to avoid a needless operation Still another patient was treated for heart disease for six months because his most conspicuous symptom was shortness of breath which was not related to his heart but was due to his anemia

Treatment —The treatment is of two types namely one to control bleeding from the local areas and the other designed to overcome the hypochromic anemia which results from loss of blood

In the treatment of nasal hemorrhages the most common type of bleeding encountered in this disease radium the actual cautery electro coagulation and various chemical caustics such as chromic acid trichloracetic acid and various others have been used Figi and Watkins (*209*) state that electrocoagulation has given better results than any other form of therapy in their hands This is usually carried out under cocainization of the nasal fossa but in a few instances a general anaesthesia has been necessary because of the patient s inability to tolerate the discomfort associated with the operation

If any anemia is present the patient should be treated with iron in the form of ferrous sulphate 0 3 gram (5 grains) in enteric coated tablets three times daily after meals If the anemia does not respond to this dosage it should be doubled If these patients continue to lose blood even in small quantities it is advisable for them to continue taking iron medication for an indefinite period

The patient may control the nasal hemorrhages by an ingenious device suggested by Hurst Hampson and Plummer (*210*) This consists of a rubber finger cot placed over a rubber catheter and tied firmly with cotton thread This is carried constantly by the patient so that when nasal bleeding occurs it can be lubricated inserted well back into the nasal cavity and inflated either by placing the open end of the catheter in

bleeding from the nose and the gastro intestinal tract may result in a severe hypochromic microcytic anemia with the production of symptoms characteristic of an anemia namely pallor, weakness dyspnea and palpitation Lesions in the stomach may cause hematemesis and the characteristic telangiectases may be observed through the gastroscope (207) Libman and Ottenberg (208) have reported a family of seven who suffered from recurrent attacks of hemoptysis in which they concluded that the general characteristics of the condition resembled chronic hereditary telangiectasia

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the patient s mouth or by a rubber bulb After the hemorrhage has stopped the cot is slowly deflated and withdrawn or allowed to fall from the nostril

It has been reported by Cope and Grover (*211*) that rutin has controlled the bleeding in a patient with epistaxes and telangiectasia of the skin There had been no change in the severity of the epistaxis and rate of appearance of new lesions in two years preceding the treatment Rutin was given in doses of 120 milligrams daily by mouth for one week, after which the daily dose was reduced to 60 milligrams In the subsequent six months of observation there was no more bleeding from the nose and no new lesions appeared on the skin or elsewhere Furthermore all of the previous lesions disappeared except two faintly telangiectatic areas requiring electrolysis and a single lesion on the wrist The authors refer to a few other cases in which favorable reports have followed the use of this preparation In general however, this drug has not been subjected to a sufficient critical trial to warrant any definite conclusions at present as telangiectatic lesions show a spontaneous tendency to variability in bleeding

Prognosis —Although these patients have a certain amount of disability from the condition and occasionally death may result from hemorrhage they ordinarily live out their usual span of life At intervals however they may be incapacitated from the effects of an extremely low hemoglobin With the modern use of large doses of iron they can be maintained in much better condition than in previous years

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CHAPTER XV

CHANGES IN LEUKOCYTES

In the following chapter a brief description of the origin morphological characteristics the numbers and the function of the various types of white blood cells will be summarized and their clinical significance evaluated

History —It is stated by Rolleston (*1*) that J B Senac (2) in 1749 mentioned the *globules blancsdupus* as belonging to the chyle and in the second edition of his *Traite de la structure du coeur* brought out in 1774 by Baron A Portal it is implied that Leeuwenhoek had seen them in the previous century In the 1783 edition of Senac s treatise however it is suggested that what the Dutch microscopist really saw were erythrocytes There does not seem to be any question but what William Hewson in 1773 did recognize the colorless blood corpuscles and assumed that they were formed in the lymphatic and thymus glands and from there poured into the thoracic duct from which they entered the general circulation He considered that they eventually reached the spleen and there were transformed into red blood cells Hewson says in 1774 (*3*)

we have proved that vast numbers of particles made by the thymus and the lymphatic glands are poured into the blood vessels through the thoracic duct and if we examine the blood attentively we see them floating in it An editorial note by Gulliver pertaining to this passage is of interest It is as follows . This passage is so clear as completely to set aside the claim made of late years by Mandl (*4*) and others to the discovery of the pale globules of the blood In that of mammalia it is quite evident that Hewson had seen these globules and considered them in all the vertebrata as lymph corpuscles a view which has recently been reviewed Senac also appears to have seen the pale globules in the blood and to have regarded them as belonging to the chyle"

A further note of additional interest by Gulliver written in 1846 (*5*) is as follows The globules of the chyle of the thymus gland and of the lymph are smaller and differ in structure from the pale globules of the blood In these last there are two three or four nuclei easily seen when the envelope is made more or less transparent or invisible by acetic sulphurous citric or tartaric acid But the globules of the chyle or lymph and of the thymous fluid like the nuclei of the red corpuscles of the blood are only rendered more distinct and slightly smaller by any of

204 Fitz Hugh T Jr Importance of Atavism in Diagnosis of Hereditary Hemorrhagic Telangiectasia *Am J M Sc* *166* 881 1923

205 Schuster N H Familial Haemorrhagic Telangiectasia Associated with Multiple Aneurysms of the Splenic Artery *J Path & Bact* *44* 29 1937

206 Rundles R W Hemorrhagic Telangiectasia with Pulmonary Artery Aneurysm Case Report *Am J M Sc* *210* 76 1945

207 Rensham R J F Multiple Hemorrhagic Telangiectasis with Special Reference to Gastroscopic Appearance *Cleveland Clin Quart* *6* 226 1939

208 Libman E and Ottenberg R Hereditary Hemoptysis *J A M A* *81* 2030 1923

209 Rice F A and Watkins C H Hereditary Hemorrhagic Telangiectasia *Proc Staff Meet Mayo Clin* *18* 118 1943

210 Hurst A F Hampson A C Plummer N S and Yates A G Hereditary Telangiectasia with Haemorrhagic Tendency *Guy's Hosp Rep* *82* 81 1932

211 Cole I I and Grover R W Use of Rutin in Hereditary Hemorrhagic Telangiectasia Case Report *J Invest Dermat* *10* 39 1948

It was Rudolph Virchow (*11*) whose attention was doubtless attracted to the white blood cells through his interest in leukemia which he described in 1845 who first appreciated the significance of an increase in leukocytes of the peripheral blood as an inflammatory reaction and introduced the term leukocytosis" "The question concerning the resemblance or want of resemblance between the colorless cells of the blood and the pus corpuscles still continues to occupy the attention of observers and it will probably still require a number of years before the views entertained with regard to the connection between the colorless corpuscles and pyanemia have been rendered so clear On page 167 Virchow states The condition in which the increased proportion of colorless corpuscles in the blood appears to be dependent upon an affection of the lymphatic glands I have designated by the name *Leukocytosis* Now you know that another matter has long been the subject of my studies the affection named by me leukaemia and our next business must be to determine how far genuine leukemia differs from these leucocytotical conditions Virchow observed that in leukemia there was not only an increase in the white blood cells but also a decrease in the erythrocytes Hence as he said so that as a final result a condition was attained in which the number of colourless corpuscles was almost equal to that of the red ones He continued to state that while in normal blood there were 300 red corpuscles to one white in leukemia the proportion may be that for every three red corpuscles there is one colourless one or even two or in which indeed the great numbers are in favour of the colourless corpuscles" Virchow also pointed out that leukemia was a fatal disease that towards the close of life a genuine hemorrhagic diathesis is developed that the spleen is constantly enlarged and often a number of the lymphatic glands He concludes by stating that leukemia is thus a sort of permanent progressive leukocytosis whilst this (leukocytosis) on the other hand in its simplest form constitutes a transitory process connected with fluctuating conditions in certain organs"

Rolleston (*1*) quotes Professor William Bulloch as stating that the word 'leukocyte" made its first appearance in 1855 in M P Littre and C Robin s *Dictionnaire de Medicine* Samuel Wilks in 1855 (*12*) examined the blood in over 50 patients most of them suffering from anemia splenic enlargement scurvy purpura and ague He did determine that in two patients with splenic enlargement (probably due to myelogenous leukemia) that the red and white blood cells were in nearly equal proportions The only case in which there was a considerable excess of white blood cells was a man dying of typhus fever It is of interest that he also examined the blood of patients of Dr Thomas Addison in whom the diagnosis of "idiopathic anemia" had been made and in them found no evidence of an increase in the white blood cells It is unfortunate for the advance of blood examinations at the time that

these acids so that the central part presents no regular nuclei or divided nucleus, such as contained in the pale globules of the blood" This comment by Gulliver in 1846 is remarkably clear in recognizing at that time the polymorphonuclear leukocytes with two, three or four nuclei and the lymphocytes

To William Addison as early as 1840 (6), must be given the credit for having made accurate observations on the white blood cells In examining the blood of two patients with acute rheumatism one with pleurisy, and one with quinsy he noted that the "inflammatory or buffy coat had two kinds of globules the heavier red globules sinking to the bottom and forming the lower portion of the clot and the colourless lighter globules swimming at the top Furthermore he viewed the circulation in the web of a frog's foot and noted three distinct forms of globules first the oval , second with a circular or rather irregular outline and third with a smaller more regular circular outline with little specks or spots" On placing a particle of salt on the web of the foot he observed that the current of blood was at first retarded and finally the round globules accumulated in the usual manner

It is of interest to note from the above statement that as early as 1840 Addison was employing a method whereby he could observe the action of the components of the blood in the live animals and also that he studied the effect of adding an irritant to the region of the small vessels to observe the change effected In 1843 William Addison noted the increase in the number of leukocytes of the blood of a patient with scarlet fever and also in blood taken from the region of a furuncle The great significance of this observation however was not appreciated and it was soon forgotten In a later publication in 1850 Addison (7) anticipated Cohnheim when he stated that in inflammatory process was characterized "by the appearance or accumulation of cell forms termed lymph particles upon and around the blood vessels Alexander Donne (8) in 1842 and also Andral in 1843 (9) described the white corpuscles To T Wharton Jones in 1845 (10) Lecturer on Anatomy Physiology and Pathology at the Charing Cross Hospital and teacher of Huxley must be accorded the credit for a clear description of the different types of white blood cells in the blood of various animals and man He states (10) Among the corpuscles in the blood of man and mammifera corresponding to the granule cells of the blood of animals are certain of those spoken of under the name of lymph or colourless corpuscles Both coarsely and finely granular stages of the granule cell may be recognized In human blood some especially those in the finely granular stage may be seen shooting out processes like the same cells in the blood of the frog This investigator states (10) that he borrowed the name granule cell from Professor Vogel of Gottingen who first employed it to designate a form of cell which is developed in inflammatory exudations

patient and reported that they were 1 640 000 and 1 660 000 per cubic millimeter He comments that a greater diversity than this would still be less than Sorenson found to be unavoidable with Malassez s instrument"

In 1892 Ehrlich had formulated (*16*) the following view concerning leukocytosis "The bone marrow is a breeding place in which immense numbers of polynuclear cells are formed from the mononuclear These polynuclear cells above all other elements have the power of emigration This power becomes immediately evident when substances chemostatic to the white elements circulate in the blood With Kurloff I regard leukocytosis as a function of the bone marrow

The Introduction of the Differential Blood Count —One of the greatest advances in modern hematology was the introduction of staining methods by Ehrlich whereby the various white blood cells could be readily recognized as belonging to the five varieties The earliest publication dealing with this subject was by Ehrlich in 1879 (*17*) At this time he says "only a few of these granules like fat and pigment are readily recognized By far the greater number are little if at all characterized by our present methods The majority of investigators are content therefore to determine the presence of the granules in certain cells and according to whether they were more or less refractive describe them as fat drops or albumin Previous experience especially with mast cells led me to suspect that these granules irresponsive to chemic investigation would become recognizable on staining i e their behavior toward certain dyes Further I found that these granules could be so characterized and was able to follow them through different animals and organs On account of their differential characteristics I would propose designating these granules specific granules

Ehrlich described his technic of spreading the blood in "the thinnest possible layer on cover glasses drying the film at room temperature and staining after a variable period He goes on to say "the sharp differentiation of acid basic and neutral stains and the corresponding oxyphile basophile and neutrophile granulations undiscovered in all previous work was the first result of this investigation It naturally required combinations repeated hundreds of times to produce the triacid solution which in its original form or slightly modified continues to play a prominent role in histologic study " It was claimed by Ehrlich from the very beginning of his studies that different varieties of cells possess distinctive granules which can be recognized not only by their behavior toward stains but likewise by their reaction toward solvents

In 1880 Ehrlich (*17*) published the article which is usually regarded as the foundation of the differential count and in 1892 (*16*) amplified his original work greatly

The Arneth Count —In 1904 Arneth (*18*) introduced the idea that the neutrophils in the circulating blood differ in health and disease and this

Wilks selected such cases for estimation of the white blood cell count as they are the type in which a leukocytosis does not commonly occur It was his opinion, therefore that leukemia is rare which of course is correct, but he infers from his experience that an estimation of the white blood cell count is not likely to be of value from a clinical standpoint in many cases Apparently he did not grasp the significance of the elevated white blood cell count in the patient with typhus fever How different might his conclusions have been if he had examined a group of patients with lobar pneumonia!

Schultze in 1865 (*13*) described four types of white corpuscles in human blood and recognized those which were finely and those which were coarsely granular In Plate 2 of his publication cell number seven appears to be clearly a polymorphonuclear cell but some of the granules are large for those of a neutrophil Earnest Haeckel in 1882 made the initial observations on phagocytosis which were elaborated in 1886 by Elie Metchnikoff at which time the latter investigator introduced the term phagocytosis

Enumeration of Leukocytes—The earliest recorded leukocyte count (*14*) was that performed by Herman Welcker on Margaret Mueller on April 25 1853 at which time it was estimated that this subject had 12 133 white blood cells per cubic millimeter Enumeration of the blood corpuscles according to Rolleston (*1*) was at first and until after Ehrlich's work in the decade of 1880–1890 estimated by their proportion to the red blood cells the normal ratio being regarded as 1 white corpuscle to 300 red blood cells This ratio is unduly low as a red blood cell count of 5 million by this calculation would give a white blood cell count of over 16 000 per cubic millimeter Potain invented the blood diluting pipette in 1867 and Gowers the modern counting chamber in 1877 In an article written in 1877 (*15*) Gowers stated that the method of counting corpuscles which had been employed in France and Germany was almost unknown in clinical medicine in England at that time He acknowledges *the introduction of the principle of counting red blood cells* as introduced by Vierordt a quarter of a century ago and refers to various modifications as introduced by Potain Malassez Hayem and Nachet He then describes the basis for the modern counting chamber which he introduced at that time He states that the average healthy person has a red blood cell count of 5 million per cubic millimeter as shown by Vierordt and Welcher but cautions that a healthy man has a somewhat higher and a woman somewhat lower count He gives some examples of the red blood cell count as in anemia from lead poisoning 3 320 000 per cubic millimeter in chlorosis 3 320 000 per cubic millimeter, in a man with idiopathic anemia the number of red blood cells was as low as 1 650 000 per cubic millimeter To demonstrate the accuracy of his method Gowers did two counts with separate dilutions in the same

In 1898 Thomas R Brown reported that an eosinophilia is so constantly associated with trichinosis that its presence constitutes an important diagnostic finding in the disease The original contribution of Brown appeared in the *Journal of Experimental Medicine* (29) but a preliminary communication on the subject had been published by William S Thayer in 1897 (30) Brown found in the blood of a patient in whom it was demonstrated that trichinae were present in the muscles that the eosinophils made up 27 per cent of the total number of leukocytes in the circulating blood Subsequently they rose on the 50th day after admission to 68 2 per cent Similar findings were demonstrated in subsequent cases

In 1902 Calvert noted that an eosinophilia was present in patients with Filaria bancrofti and in the same year that such a change occurred in the blood of patients affected with Bilharzia hematobium (31)

An excellent review with the early literature is given by Zappert in 1893 (32)

The Normal Number of Leukocytes in the Circulating Blood—It is generally accepted that the normal number of white blood cells in the circulating blood of the adult varies between 6000 and 10 000 per cubic millimeter From my experience however two modifying statements should be made in regard to this First it is recognized that leukocyte counts as low as 5000 per cubic millimeter are not uncommon in apparently healthy individuals and hence the lower limit of normal should certainly be reduced to that level It is also true that counts even lower than this occur occasionally in normal individuals without having clinical significance While preparing a paper dealing with the causes of leukopenia (33) I considered it advisable to lower the limit of the normal white blood cell count to 4000 per cubic millimeter in order to be more certain of including only those cases in which the white blood cell count could be regarded as abnormal beyond the slightest question of a doubt From my experience therefore I would consider a count of 5000 per cubic millimeter to be the lower limit of normal and I would not attach too much significance to one of 4000 per cubic millimeter unless there were other important clinical manifestations associated with it Second slight transient increases above the commonly accepted level of 10 000 per cubic millimeter cannot always be regarded as indicating pathological conditions It has been found for example that 11 per cent of apparently normal persons have a count which is above this figure (34) Such slight increases above 10 000 per cubic millimeter are in most cases due to the normal or physiological variations which will be discussed below (pages 697 to 705)

Errors in Counting White Blood Cells—It is amazing to witness in some instances the unquestionable acceptance of information often furnished by the most inexperienced intern with regard to the level of the white blood cell count This is all the more remarkable because it

difference is especially prominent in acute infections. It was his belief that the changes in the cell were largely confined to the nucleus and that the differential count alone failed to give complete information concerning the reaction of the body to infection. It was his contribution to the field of hematology that in normal individuals the nuclei of the neutrophils contain from one to five segments, those with three to four predominating. Furthermore he believed that there is a constant relationship between the number of cells with non segmented nuclei and those with two or more lobes. The type of the nucleus in the neutrophils he considered was an indication of their age, namely, the greater the number of the lobes the older the cell. In acute infections there is a "shift to the left" (Linksverschiebung) indicative of an increase in the number of young neutrophils, whereas when the infection subsides there is an increase in the number of cells containing many lobes or a shift to the right (Rechtsverschiebung). Arneth's original formula was unnecessarily complex, involving five different classes of neutrophils. Shortly after it was introduced there were many modifications suggested in an attempt to simplify it. For a full discussion of these the reader is referred to the monograph by Muller (19).

Of the various modifications, the ones introduced by Schilling in 1911 (20), Cooke and Ponder in 1927 (21), and the filament nonfilament count first suggested by Farley, St Clair and Reisinger in 1930 (22) are the more important.

The Eosinophil.—It is probable that Wharton Jones in his pioneer studies of 1846 (10) observed eosinophils when he noted colorless leukocytes with coarse granules. These granules attracted the attention of Ehrlich who demonstrated that they were not only stained with acid dyes but furthermore they possessed such an affinity for eosin that when treated with various mixtures made up of this stain without acid dyes they took up the eosin alone. Eosinophil leukocytes were discovered in the blood of man and other mammals and in the frog. It was discovered by Hirschfeld (23) that coarse acidophil cells were characteristically present in the blood of all mammalian species examined by him.

The first disease in which it was demonstrated that there was an increase in these cells was leukemia. This was observed by Ehrlich. An eosinophilia was first noted in asthma by Gollasch in 1889 (24), in pemphigus in 1892 by Neusser (25), in acute and chronic skin disease in 1892 by Canon (26), and in helminthiasis by Muller and Rieder (27) in 1891. These two observers found an eosinophilia of 8.2 and 9.7 per cent respectively in two men with Ankylostomum duodenal infestation. This led to a thorough investigation of the blood in patients harboring many types of intestinal worms by Bucklers (28) who discovered that an eosinophilia was characteristic of many other infestations with intestinal parasites such as Strongyloides intestinalis, Ascaris lumbricoides, Taenia solium and Taenia saginata.

number were 16 000 per cubic millimeter it might be within the range of 15 000 to 16 700 per cubic millimeter The errors which are recognized to occur in the differential count of the leukocytes are discussed on page 709

The Physiological Variations in the Leukocytes—Nature of the Changes—It is known that irregular and sometimes pronounced fluctuations occur in the total white blood cell count in normal persons These are called physiological variations because they have no pathological significance but sometimes they are falsely interpreted as being of diagnostic importance The changes are most frequently 1 within the range of so called normal that is from 5000 to 10 000 cells per cubic millimeter but this is not always the case 2 the fluctuations are often associated with an increase in the percentage and absolute numbers of the mature polymorphonuclear leukocytes but they may also affect the lymphocytes and 3 the apparent increase in the number of white blood cells in the circulation is due in most instances to the redistribution of these cells in the vascular channels of the body

Spontaneous Variations Throughout the Day—It has been shown by Garrey and Bryan (*34*) that when leukocyte counts are done in the morning under basal conditions a great majority of the white blood cell counts will range from 5000 to 7000 cells per cubic millimeter According to these observers the minimum count is present early in the morning under conditions of rest at which time it varies least Furthermore they state that after an hour of recumbent rest in the afternoon 90 per cent of all leukocyte counts fall within the limits of the morning basal counts In a careful study Kennon Shipp and Hetherington (*38*) determined the white blood cell count of six young men at intervals of 15 minutes throughout the day for periods varying from five to seven hours on two successive days They observed 1 That the total number of leukocytes varied from count to count due to changes in the granulocytes but no evidence of a rhythm could be determined as claimed by Sabin Cunningham Doan and Kindwall (39) 2 The undulations in the curve had a tendency to adhere to the same pattern in a given subject on successive days 3 After a rest of from one half to one hour there was a fall in the leukocyte count to the basal range 4 There was no significant alteration in the white blood cell count when the erect posture was assumed 5 The apparent spontaneous variations in the white blood cell count throughout the day were slight usually the difference being between 100 and 400 cells between the highest and lowest counts but in one instance the maximum variation was 900 and in another 1800 per cubic millimeter 6 While there was no steady consistent rise in the white blood cell count in the afternoon in all instances there was a steady post meridian peak between 12 00 noon and 3 00 P M and 7 Although the subjects had breakfast or a light lunch during the days of the study there was no evidence of a digestive leukocytosis

sometimes has a highly important bearing on the diagnosis and not infrequently the surgical treatment of the condition Clinicians have often been admonished to beware of information that can be set down in a definite figure because it *appears* to be so dependable It is no better however than the method by which it was obtained and therefore should be evaluated carefully in each case Certainly before radical decisions are made the information should at least be checked In my earlier clinical experience the hematological data furnished by the average intern was much less dependable than at present, but it is still subject to considerable error and hence all such results should be scrutinized by the critical eye of the experienced clinician who should readily detect inaccurate reports The more accurate results now furnished are not entirely due to the employment of standardized hemacytometers and pipettes but also because the interns throughout the country received better training in laboratory technic

The sources of error in the white blood cell count may be divided into two types namely 1 that due to the inexpertness of the examiner which is obviously of considerable extent in some laboratory workers, and 2 anticipated technical errors which are inherent in the method In the following discussion therefore the technical errors only will be discussed and it is assumed that the counts are made by the most expert technicians

It has been pointed out by Bryan Chastain and Garrey (35) that the most important technical errors are those which are dependent upon three factors 1 mixing of the cells and diluting fluid 2 filling the counting chamber by capillarity and 3 settling of cells by chance on the ruled field of the counting chamber It was their opinion that the chance settling of cells is responsible for all of the *major errors* of subsampling Based upon an analysis of 2508 white blood cell counts they report an average error of ±241 ±35 per cubic millimeter when *10 unit* hemacytometer areas of one square millimeter each and a dilution of 1 to 20 are employed The magnitude of this error does not alter appreciably at the different levels of the observed leukocyte counts as shown by the low value of the probable error It has been shown by Plum (36) that $e = N$ where e = the mean error and N = the number of cells counted As Wintrobe (37) points out the mean error may amount to as much as 600 cells when the leukocyte count is normal (7000 per cubic millimeter) and an area of 4 square millimeters (one chamber) is counted or 425 cells if the count is made in two chambers or 8 square millimeters By his calculations when the count is 16 000 per cubic millimeter the probable error would be 900 if the count is made in one chamber only Hence in the hands of an expert technician if the actual count were 7000 per cubic millimeter the permissible error would allow a range in the total count of 6400 to 7600 per cubic millimeter and if the actual

respond to short severe exercise whereas following prolonged exertion the leukocytosis is of the polymorphonuclear type

It is of interest to note that leukocytosis may be associated with an accelerated circulatory rate even though the patient is otherwise at rest It is reported by Levine and Golden (*44*) that in eleven patients with paroxysmal rapid heart action in whom the heart rate varied between 130 and 250 per minute for two hours to twelve days in six the leukocytosis ranged from 13 000 to 22 000 per cubic millimeter

Effect of Emotions on the Leukocyte Count—It is claimed by some that emotions of fear rage and apprehension may raise the count to muscular activity levels and this seems a plausible assumption provided these emotions increase the circulatory rate sufficiently Such changes are reported by Garrey (*45*) but Edwards and Wood (*43*) consider that excitement alone is without effect on the leukocyte count This they demonstrated by determining the leukocyte count on spectators at athletic contests football players immediately prior to participation in games and track athletes just before a race

Leslie and Zwemer (*46*) were unable to cause an increase in the leukocyte count in cats from emotional stimulus in the absence of muscular activity On the other hand Milhorat Small and Diethelm (*47*) observed a leukocytosis in proportion to the emotional reaction in patients with various types of psychiatric disorders Fear agitation or anger characterized the emotional states associated with leukocytosis It appears therefore that a leukocytosis may or may not be associated with various emotions Perhaps the differences in the reports can be reconciled on the basis that a leukocytosis is associated with emotional upsets in proportion to the amount of associated physical activity and therefore the degree to which the circulatory rate is increased

The Effect of the Digestive Processes on the Leukocyte Count—Whether or not there occurs a leukocytosis attributable to the digestive processes is still a controversial question The general consensus at the present time however is that the changes in the total number of circulating white blood cells during the day are independent of the ingestion of food Wintrobe (*37*) states that "digestion of food probably does not cause appreciable leukocytosis as was formerly the opinion" The very extensive literature dealing with this subject is reviewed by Arneth and Ostendorf (*48*) and Garrey and Bryan (*34*)

The Leukocyte Count in Pregnancy, Labor, and Puerperium—Most observers report that the leukocyte count is slightly elevated during pregnancy the increase being due to greater numbers of neutrophils and of these there is a larger percentage of younger forms than is found in nonpregnant women The subject is reviewed by Sturgis and Bethell (*41*) The blood studies carried out by Bethell Hartsuff and Farrell (*49*) indicate that the following changes occur during pregnancy 1 The total

The Effect of Muscular Exertion on the Leukocyte Count.—It appears to be clearly established that the leukocytes increase in numbers in the circulating blood following muscular exertion. This is a contant finding and, furthermore, it is generally accepted that the leukocytosis to a certain extent *is proportional to the duration and severity of the muscular contractions*. Reviews of the literature bearing on this subject have been published by Grawitz *(40)*, Garrey and Bryan *(34)*, and Sturgis and Bethell *(41)*.

As long ago as 1893 it was shown by Schulz *(42)* that marathon *runners at the termination of the race* had a leukocytosis which varied from approximately 14,000 to 27,000 cells per cubic millimeter with a percentage of polymorphonuclear leukocytes which ranged from 80 to 90 per cent. It is now generally believed that the leukocytosis is due to a redistribution of cells in the body rather than an actual formation of new cells. This is indicated by the rapidity with which the increase may occur and by the fact that only a small percentage of the cells are of the younger types. It is known, for example, that at the termination of a quarter mile race of less than a minute's duration, the white blood cell count may be as high as 35,000 per cubic millimeter. It is generally accepted that the changes in the leukocytes in the circulating blood following exercise are due to circulatory shifts with the liberation of sequestered leukocytes from unused capillaries through the body. These reservoirs in which the polymorphonuclear cells are stored may be in various organs and tissues of the body such as the spleen, liver, lungs, glands of internal secretion, bone marrow, and muscles.

That the extent of the leukocytosis is directly proportional to the amount of exercise is shown by the studies of Edwards and Wood *(43)* who noted an increase of nearly 300 per cent in the white blood cell counts of football players although the actual duration of play of any single player in a 60 minute game is only eight minutes. These observers found that after playing one quarter of the game the average white blood cell count was 12,000 per cubic millimeter, after one half 15,500, after three quarters 18,000, and after having completed the entire game 23,000.

The increase in the white blood cells during exercise may be due either to a greater proportion of granulocytes or lymphocytes. Apparently the response in any given person following exercise depends on the release of cells from two reservoirs in the body. One of these is the reserve supply of polymorphonuclear leukocytes sequestered in the inactive capillaries of the body. The other is the segregation of lymphocytes in the lymphatic system. Cells of both types are returned to the circulating blood following muscular activity but in one person the lymphocytes may be swept into the circulation first while in another it may be the polymorphonuclear cells. In general, it is now believed that the lymphocytes more commonly

TABLE XXIX

Age (Weeks)	Number of Counts	Leukocyte (Thousands per Cu Mm) Mean	Standard Deviation
3 d	16	14.[illegible] ± 0.77	3.08 ± 0.54
11th	0	10.79 ± 0.62	2.77 ± 0.44
23rd–25th	[illegible]0	13.41 ± 0.6[illegible]	2.77 ± [illegible].44
49th–52nd	20	12.8[illegible] ± 0.72	3.23 ± 0.51

Leukocyte counts during first year of life
(Magnusson Courtesy *Acta paediat.*)

5750 to 12,200 per cubic millimeter. In all of these women a rise averaging about 2000 cells per cubic millimeter was noted after the onset of labor as compared with the previous counts. As labor progressed the leukocyte counts increased to maximum average levels of 22,250 and 15,270 per cubic millimeter in the cases of primiparae and multiparae respectively. There was no further increase in the counts in the third stage of labor. By the seventh day of the puerperium the white blood cell counts gradually returned to normal. In explaining the leukocytosis it is concluded by Wolff (52) that the work of the contracting uterine muscle appears to stimulate the mobilizing of the polymorphonuclear leukocytes into the systemic circulation.

Variations of the Leukocyte Count with Age.—The leukocyte count shortly after birth varies between 15,000 and 25,000 per cubic millimeter with the average being closer to the smaller figure. There is rather an abrupt fall to about 14,000 per cubic millimeter at the tenth day of life with a subsequent gradual decline throughout infancy and childhood. The literature dealing with the leukocyte count early in life is reviewed by Magnusson (53) and he presents his own observations which are shown in Table XXIX.

There is some variation in the figures regarding the normal leukocyte counts in children which may be due to the inadvertent inclusion of some subjects with subclinical pathological process which might cause either a leukocytosis or a leukopenia depending upon the etiological agent.

At birth the neutrophils are the predominant white blood cells in the circulating blood but during the second week their count falls rapidly and they are exceeded by the lymphocytes. Although the latter cells decline in numbers they remain the predominating cell until about the fourth year when they are surpassed by the neutrophils. Eosinophils and basophils remain at a relatively uniform level throughout infancy, childhood, adolescence and adult life. These findings as observed by recent authors are given in Table XXX.

The Effect of High Altitude and Solar Radiation.—It has been claimed that persons residing at high altitudes have a relative lymphocytosis. This might be explained on the basis that they receive more ultraviolet radia-

TABLE XXVIII

LEUKOCYTE VALUES IN PREGNANCY, THE PUERPERIUM AND AT APPROXIMATELY ONE YEAR AFTER DELIVERY

(Bethell, Hartsuff and Farrell, 1943)

	Leukocytes (Thousands/Cu. Mm.)			*Differential Counts (Mean Percentages)*					
Month of Pregnancy	*No. of Subjects*	*Mean*	*S.D.*	*No. of Subjects*	*Neut.*	*Eos.*	*Bas.*	*Lymph.*	*Mono.*
2nd	11	10.182	2.886	10	58.00	2.90	0.00	34.00	4.90
3rd	46	10.022	2.445	41	66.71	1.67	0.17	27.85	3.93
4th	81	10.420	2.154	79	67.66	2.17	0.11	27.51	3.35
5th	125	10.889	3.112	114	67.72	1.63	0.15	26.96	4.11
6th	154	10.539	2.543	147	69.56	1.49	0.12	25.21	3.98
7th	200	10.875	2.435	1[illegible]8	69.69	1.39	0.15	25.30	4.41
8th	22[illegible]	10.518	2.975	190	69.47	1.58	0.12	25.11	4.4
9th	1[illegible]4	10.339	2.515	149	68.96	1.52	0.09	25.32	4.4[illegible]
Postpartum									
5th–9th wk.	343	8.192	1.858	334	51.[illegible]9	2.84	0.31	41.28	4.26
10th–14th month	111	8.072	0.610	107	54.[illegible]3	2.54	0.26	39.52	3.83

(Sturgis and Bethell. Courtesy *Physiological Review.*)

leukocyte count remains slightly elevated throughout pregnancy with an average count which is usually between 10,000 and 11,000 per cubic millimeter. 2. There are relatively minor changes in the total leukocyte count from month to month. 3. There is persistent neutrophilia which does not exceed 70 per cent and one which reaches a peak during the seventh month of gestation and then undergoes a slight decrease, and 4. Lymphocyte, eosinophil and basophil percentages are lower than in non-pregnant females but the absolute values for these cells are but little affected during gestation. The percentage of monocytes does not change but their absolute number increases during pregnancy. The range of the total number of leukocytes is great throughout pregnancy as indicated by the high figures which are obtained for the standard deviations. The total white blood cell count declines and becomes more uniform at the fifth and ninth weeks postpartum, the decrease being at the expense of the neutrophils. A summary of the findings during pregnancy as observed by Bethell, Hartsuff and Farrell are given in Table XXVIII.

It has been determined by a number of observers that the leukocyte count rises during parturition, the average increase being between 1500 and 2000 cells per cubic millimeter (*50, 51, 52*). The earlier publications dealing with this subject have been reviewed by Wolff (*52*) who reports his own observations on 50 women who were studied shortly after the onset of labor until the conclusion of the hospitalization period of 8 days. The average white blood cell count of these women during the last week of pregnancy was 6054 cells per cubic millimeter with a range from

TABLE XXX A

LEUKOCYTES

Age	(Thousand per Cu Mm)	
	Mean	Range
At Birth	18 1	9 0–30 0
End 12 Months	11 4	[illegible] 0–17 5
End 4 Years	9 1	5 5–15 5
End 10 Years	8 1	4 5–13 5
End 16 Years	7 8	4 5–13 [illegible]
End 21 Years	7 4	4 5–11 0

TABLE XXX A—Showing total leukocyte count in thousands per cubic millimeter in man from birth to maturity Based on data collected and arranged by [illegible] C Albritton (*Standard Values in Blood* Philadelphia and London W B Saunders Co 1952)

light had an average of 54 2 per cent of polymorphonuclear cells and one of 39 7 per cent of lymphocytes in the circulating blood An average of 54 36 for the neutrophils and 36 2 for the lymphocytes in the blood of persons living in Butte Montana which has an altitude of 5775 feet and a sunlight percentage of 57 has been reported by Peterson and Peterson (56) It is reported by Albritton (57) that at sea level (Lima Peru) the lymphocyte percentage in a group of normal adults was found to be 29 8 at Oroya Peru altitude 3730 meters it was 34 8 per cent and at Morococha Peru altitude 4500 meters it was 39 4 per cent The total white blood cell count at these three levels in the group examined remained the same

It must be concluded therefore that changes in the leukocytes attributable to high altitudes and increased sunlight show only slight deviations from the generally accepted normal values although the trend of such figures appears to be suggestive

Variations in the leukocytes in relation to meteorological alterations have been studied by Berg (58) It has been reported by Petersen and

TABLE XXX B

RELATIVE AND ABSOLUTE VALUES FOR LEUKOCYTE COUNTS IN NORMAL ADULTS PER C MM BLOOD

Type of Cell	Per Cent	Absolute Number		
		Average	Minimum	Maximum
Total Leukocytes		7000	5000	10 000
Myelocytes	0	0	0	[illegible]
Juvenile Neutrophils	3 5	300	150	400
Segmented Neutrophils	54–62	4000	3000	5 800
Eosinophils	1–3	200	50	250
Basophils	0–0 75	25	15	50
Lymphocytes	25 33	2100	1500	3 000
Monocytes	3–7	375	285	500

(Wintrobe *Clinical Hematology* Courtesy Lea & Febiger)

TABLE XXX

MEAN LEUKOCYTE VALUES AT DIFFERENT AGES*

Age	Author	Total W B C (000/Cu Mm)	Neutrophils (Per Cent)	Eosinophils (Per Cent)	Basophils (Per Cent)	Lymphocytes	Monocytes
Newborn	Poncher* 1943	25 000	60 0	2 5	0 5	22 5	10 0
	Chuinard***1941	15 000	60 0	3 0	0 5	30 0	5 0
10th day	Poncher*	14 000	40 0	2 5	0 5	42 5	7 0
	Chuinard **	8 000	43 0	3 0	0 5	45 0	5 0
4th–6th month	Poncher**	12,000	32 0	2 5	0 5	52 5	4 0
	Magnusson 1938	13,410	24 18	3 09	[illegible] 21	64 16	7 3
	Bethell 1943	11 279	25 0	1 80	0 15	[illegible]	3 61
10th–12th month	Poncher *	9 000	32 0	2 5	0 5	57 0	4 0
	Magnusson	12 820	29 52	2 54	[illegible] 25	60 63	6 41
	Bethell	12 358	28 62	2 46	0 14	65 54	3 65
	Suzuki** * 1937	11 000	27 5	2 0	6	62 5	5 0
4th year	Poncher*	9 000	42 0	2 5	0	45 0	4 0
	Osgood* * 1939	10 400	41 0	3 0	0 5	48 0	3 0
	Suzuki* *	8 500	45 0	2 5	0 6	45 0	5 5
7th year	Poncher**	8 000	50 0	2 5	0 5	33 0	4 0
	Osgood*	10 400	41 0	2 0	0 5	48 0	3 0
	Suzuki** *	8 000	50 0	2 5	0 6	40 0	5 5
12th year	Poncher**	[illegible] 000	52 0	2 5	0 5	28 0	4 0
	Osgood* *	8 400	41 0	2 0	0 5	48 0	3 0
	Suzuki	7 000	60 0	3 0	0 7	30 0	6 0
15th year	Osgood	8 400	51 0	2 0	0 5	42 0	4 0
	Suzuki****	[illegible] 500	65 0	3 0	0 7	23 0	6 0
Adult	Osgood* *	7,400	55 0	2 0	0 5	38 0	4 0
	Suzuki*	6 000	67 0	3 0	0 7	23 [illegible]	6 0

* It has not been possible to establish statistically comparable ranges for the data included in this table It is designed to indicate the trend of change throughout infancy and childhood Apparently healthy individuals especially in infancy may give values differing widely from the means Where the summation of the percentages falls appreciably short of 100 the discrepancy is due to omission of unidentified and disintegrated cells The numbers of observations from which these figures were derived are comparatively large with the exception of those of Magnusson This author however chose his subjects with special care and subjected his data to detailed statistical analysis

** Approximate values calculated from authors ranges

* * Smoothed means with some new values adapted from the authors classification to fit the present table

* * Data largely compiled from the reports of many authors chiefly in the Japanese and German literature

(Sturgis and Bethell Courtesy *Physiological Reviews*)

tion which has been shown by Clark (54) to stimulate a relative lymphocytosis In 1933 Stammers (55) observed that persons living in Johannesburg South Africa with an altitude of 6000 feet and 73 per cent of sun

during the first or second hours of treatment This was due to the diminution in the number of neutrophils Following this there was a constant elevation in the number of leukocytes in which the maximum amounting to approximately 30 per cent of the initial figures occurred about the sixth to the ninth hour The magnitude of the leukocyte response was proportional to the height and duration of the temperature rise but the greatest increase in the count occurred several hours following the return of the body temperature to normal The highest leukocyte count recorded was 22 600 per cubic millimeter As the rise was due mainly to an increase in the total numbers of the neutrophils to which the staff (nonfilamented) cells contributed the greatest increment usually being between 200 and 300 per cent it was concluded that the total leukocyte increase was due to a stimulation of the bone marrow While this may be the case nevertheless it should be kept in mind that the accelerated circulatory rate which accompanies the hyperpyrexia must also contribute something to the leukocyte count by causing a redistribution of the white blood cells It is stated by Bierman and Fishberg (*62*) that during hyperpyrexia the velocity of the circulation may be increased more than 400 per cent

Displacement Redistribution, or Pseudoleukocytosis —Throughout the section dealing with the physiological changes in the number of leukocytes repeated reference has been made to the role played by a redistribution of the leukocytes in altering the numbers of these cells in the circulating blood Such a process does not change the total number of white blood cells in the body but merely indicates that they have been redistributed

The entire subject is reviewed in a scholarly and comprehensive manner by Vejlens (*63*) His observations indicate that normally in the veins some of the white corpuscles are axial flowing and others are marginal and adherent to the vessel wall The latter are always neutrophils It is his opinion that an increase or decrease in the total number of marginal neutrophils is the main reason for the physiological changes in the total number of leukocytes in the circulating blood Undoubtedly this is an important factor but it disregards the fact that the changes attributed to redistribution may be due in part at least to the redistribution of the lymphocytes caused probably by an increased flow of lymph as observed following exercise

Vejlens considers that the position of the leukocytes in the blood stream of the small veins is dependent upon two chief factors first alterations in the circulatory rate and second variations in the suspension stability of the blood plasma which is probably related partially to its fibrinogen content According to this theory a decrease in the white blood cell count results when there is a reduction in the rate of blood flow and consequently neutrophils remain in the marginal position and become

TABLE XXX C

	Mean Percentage	Standard Error of Mean	Standard Deviation of Series	Coefficient of Variation
Neutrophils	56.88	±1.201	±5.886	10.4
Eosinophils	2.01	±0.209	±1.023	50.9
Basophils	0.44	±0.042	±0.204	46.5
Lymphocytes	37.03	±1.221	±5.982	16.2
Monocytes	3.64	±0.168	±0.825	22.7

(Sturgis and Bethell Courtesy *Physiological Reviews*.)

TABLE XXX D

Age	Neutrophils Mean (%)	Eosinophils Mean (%)	Basophils Mean (%)	Lymphocytes Mean (%)	Monocytes Mean (%)
At Birth	61	2.2	0.4	31.0	5.8
End of 12 Months	31	2.6	0.4	61.0	4.8
End of 4 Years	42	2.8	0.6	50.0	5.0
End of 10 Years	54	2.4	0.5	38.0	4.3
End of 16 Years	57	2.6	0.5	35.0	5.1
End of 21 Years	59	2.7	0.5	34.0	4.0

TABLE XXX D.—*Showing percentage of different white blood cells in circulating blood from birth to maturity. Based on data collected and arranged by F. C. Albritton (Standard Values in Blood.* Philadelphia and London: W. B. Saunders Co., 1952.)

Berg (*59*) that the average white blood cell counts are higher in winter than those in summer, while the degree of fluctuation is greatest in the latter season.

Heat and intense solar radiation are factors common to the subtropical climate of Iraq in which the leukocyte picture in healthy British soldiers was studied by Kennedy and Mackay (*60*). They made the following observations: 1. There is a relative reduction in the number of neutrophils, the mean being 56.6 with a minimum of 35 and a maximum of 73.7 per cent. 2. The monocytes are increased, the mean being 13.7, the minimum being 1.0 and the maximum 29.5 per cent, and 3. The polymorphonuclear index showed a shift to the direction of immaturity. The average white blood cell count was found to be 8760 per cubic millimeter. It is their belief that heat can produce a temporary but not a sustained increase in the leukocyte count.

It is known that hyperpyrexia may be responsible for rather striking changes in the white blood cell count. At first a leukopenia is produced which is followed shortly thereafter by a polymorphonuclear leukocytosis. The effect of hyperpyrexia on the white blood cell count was studied by Bierman (*61*) in patients in whom a febrile rise to 103 to 104 degrees (F.) was induced and maintained for three or four days by radiation with a wave length of about 30 meters. The initial change was a reduction in the total leukocyte count of about 25 to 30 per cent which occurred

body production by these cells was dependent on the phagocytic activity of the leukocytes and macrophages for the assimilation of antigenic material before any antibody production could occur They emphasize that the entire problem has gained a much wider prospective since antibodies have been identified as beta and gamma globulins (*66 67*) In the authors opinion the synthesis of immune globulins will in all probability be associated with plasma globulin metabolism It is their belief based upon the experiments on rabbits immunized by intravenous injections of para typhoid vaccine that the evidence clearly refutes the idea of antibody production by *mature* lymphocytes" They do consider that the *lymphoblastic cells* of Malpighian corpuscles may be involved in antibody production to some extent In general however they emphasize that support is provided for the hypothesis that these antibodies are produced in the first instance by immature plasma cells

Effect of Epinephrine on the White Blood Cell Count—The effect of injection of epinephrine on the leukocyte counts of normal subjects has been investigated many times but new information is being collected especially since it is known that the injection of adrenocortical hormone and adrenocorticotrophic hormone produces changes in the leukocytes The previous literature of the effects of epinephrine on the leukocyte count in the circulating blood has been reviewed by Garrey and Bryan (*68*) and by White Ling and Klein (*69*) The latter authors found that after injecting 0 25 to 0 5 milligram of epinephrine subcutaneously in subjects the neutrophils rose steadily for three and one half hours The small lymphocytes increased in number during the first half hour and then fell below normal and finally returned toward normal The eosinophils rose at first and then fell below normal for the remainder of the period They conclude that the changes produced by epinephrine are similar to but not identical with those produced by adrenocortical hormone or the adrenocorticotrophic hormone

The studies of Bierman and his associates (*70*), employing the simultaneous sampling of the venous and arterial sides of the pulmonary circulation in man have led them to conclude that the initial phase of the leukocytosis and thrombocytosis following the intravenous injection of epinephrine is primarily from the pulmonary circulation It is their opinion that the pulmonary circulation in man is a sizable reservoir of leukocytes and platelets which may be discharged into the systemic circulation following the proper stimulation

It was found by Saunders and Adams (*71*) that following the injection of adrenal cortical extract and ACTH there was a reduction in the number of circulating lymphocytes and eosinophils in normal persons These same changes were observed in patients with infectious mononucleosis after comparable doses Patients with chronic lymphatic leukemia however failed to respond with a decrease in lymphocytes although

attached loosely to the vessel wall With an increased circulatory velocity the number of neutrophils adherent to the walls of the small veins is diminished, and as they soon enter the general circulation again the leukocyte count is increased The relationship if any of the changes in the suspension stability to leukopenia is less clear It is possible that in certain infections there is an increase in fibrinogen which might cause a marginal position of the neutrophils in the veins and thereby be one which might explain a factor responsible for leukopenia in some instances

Relation of Leukocytes to Immune Bodies—The relation of the white blood cells to the production of antibodies has been the subject of many clinical and experimental studies but still is unsettled and remains a controversial subject There are no uniform conclusions concerning the matter at present The evidence suggests however, that the white blood cells certainly play an important role in the defense mechanism of the body against infection not only because the neutrophils have the capacity to phagocytose and destroy pathogenic bacteria but also because these cells are closely related to antibody formation Whether this function is one attributable to the reticuloendothelial cells the lymphocytes the plasma cells or a combination of two or more of these cells is still uncertain

A comprehensive experimental study of the relationship of the lymphocyte to immunologic processes in the cat has been made by Craddock Valentine and Lawrence (64) They emphasize that many and diverse sites of antibody formation have been implicated by different observers including the reticulo endothelial tissue the lymphocytic tissue and its product the lymphocyte and the plasma cell They also give a review of the theory of the pituitary adrenal cortical control of the lymph tissue and function In their opinion all evidence favors the view that the increased availability of C_{11} oxygenated adrenal cortical steroids is associated with definite degenerative changes in lymphoid tissues There is disagreement however concerning the influence of these hormones on the functional capacity of lymphoid tissue The experiments of the above authors were designed to throw light on some features of antibody production by lymphoid tissues and its transport to the circulating blood by lymphocytes Their observations on animals are fully described in the authors original article The results did not give a final answer to all of the questions involved The authors did conclude however that under the conditions of the experiment no evidence of lymphocytic transport of antibodies to the blood was found

A review of the present day theories concerning production of antibodies and a presentation of their own experimental studies on animals is given by Keuning and van der Slikke (65) They emphasize that for a long time the reticuloendothelial system has been regarded as the site where antibodies are formed This included the assumption that anti

Errors in Determining the Differential White Blood Cell Count—It is amazing how frequently the results of a differential white blood cell count are accepted in clinical medicine after the examination of only 100 white blood cells. The figures thus obtained are assumed to be so highly accurate by some clinicians that sweeping and radical conclusions may be drawn from them. Here, as in other circumstances in medicine, we are so often misled by being able to record the result of a laboratory examination as a definite figure which we assume, at least subconsciously, is a definitive one.

The error in differential white blood cell counting should always be kept in mind when the figures for this procedure are evaluated. Barnett (78) has calculated the unavoidable error by the application of Bernoulli's theory, $SD = \sqrt{NPQ}$, where SD is the standard deviation, N the total number of cells counted, P is that fraction of the total made up of the particular cell type in question, and Q is that fraction of the total composed of all the remaining cells. This observer constructed a chart showing that if 100 cells were counted and 50 per cent were neutrophils the standard deviation would be 5 per cent and the maximum error 15 per cent. When the total number of cells enumerated was 400 instead of 100, the respective values were halved. He concludes that the total number of cells counted should be at least 400 in order to obtain reliable results in the differential count.

Studies bearing on the reliability of the differential count have been made by Goldner and Mann (79) which led them to conclude that for leukocyte percentages based upon a total count of 200 white blood cells the maximum variation is 6 per cent when the white blood cell percentages range between 30 and 70 per cent.

Although a number of different authors have widely varying opinions, it is the conclusion of most experienced observers that films made on glass slides show a distinct predominance of neutrophils and monocytes at the edges and tail of the preparation. Furthermore, when slides are used even with a well standardized technic, this inequality of distribution varies with the concentration of the red blood cells and the number of leukocytes in the blood.

It is certainly my opinion that cover slip preparations, which I have employed for almost 40 years, when only the weight of the cover slip is used to effect the spread of blood, permit the more nearly uniform distribution of white blood cells. From my experience, therefore, I recommend that at least 200 cells of a cover slip preparation be counted and that no importance be attached to alterations in the number of neutrophils unless they exceed 5 to 10 per cent. From the studies of Goldner and Mann (79), if 200 cells are counted when the polymorphonuclears are found to be 70 per cent, one may expect to find in 19 out of 20 times

the dose was doubled. One patient with Addison's disease responded with a more prominent lymphopenia than in any of the normal subjects studied. There were no changes in the heterophile antibody titers in *patients with infectious mononucleosis or normal subjects* within eight hours following the administration of ACTH or adrenal cortical extract.

The Effect of Adrenocorticotrophic Hormone (ACTH) on the Circulating Leukocytes.—It has been clearly established by the original studies of Dougherty and White and Reinhardt, Aron, and Li (*72, 73, 74*) that the numbers of leukocytes of the circulating blood are influenced by the cortex of the adrenal gland. An extensive study of the effects of ACTH on the peripheral blood has been made by Hills, Forsham, and Finch (75). They observed that when this substance is administered in a single dose of 25 milligrams subcutaneously to human subjects with unimpaired adrenal function, there is a characteristic alteration in the leukocytic pattern. *This consists of an increase in the neutrophils and a decrease in the circulating lymphocytes and eosinophils.* It is established that the decrease in the lymphocytes and eosinophils is dependent on a functionally intact adrenal cortex. The neutrophilic response is present, however, but is somewhat diminished in adrenal insufficiency. When ACTH is given over a four day period in a dosage of 10 milligrams every six hours, there is a striking elevation of neutrophils and depression of eosinophils, whereas the lymphocytes, after an initial depression persisting 24 hours or less, may rise to their former levels despite the continued increased secretion of adrenal hormones. The changes produced by cortisone (11-dehydro-17-hydroxycorticosterone, 75 milligrams every six hours) are essentially the same as those due to ACTH.

The Normal Differential White Blood Cell Count.—Although there are some minor variations, the standard number of the different types of white blood cells have been fairly well established. The following table, taken from Wintrobe (76), gives the relative and absolute values for leukocyte counts in normal adults per cubic millimeter of blood.

Further data giving the average differential white blood cell counts in young male adults between the ages of 19 to 28 years, whose blood was examined in the early spring, is given by Mainland and his associates (77). These percentage figures are based upon a total count of 2100 leukocytes for each subject.

	Mean Percentage	*Standard Error of Mean*	*Standard Deviation of Series*	*Coefficient of Variation*
Neutrophils	56.88	1.201	[illegible].856	10.4
Eosinophils	2.01	0.209	1.023	50.9
Basophils	0.44	0.042	0.204	46.5
Lymphocytes	37.03	1.221	5.982	16.2
Monocytes	3.64	[illegible].168	0.825	22.7

Beta glucuronidase has been found in the buffy layer of human blood. Most of the activity is considered to be in the leukocytes instead of the platelets with the amount evenly divided between the polymorphonuclear leukocytes and the lymphocytes. It is thought that the function of the enzyme is largely concerned with hydrolysis of glucuronides. The literature on the subject has been reviewed by Rossiter and Wong (89).

In a review of the subject, Valentine (80) emphasizes that morphologically identical leukocytes may have different metabolic patterns under varying physiological and pathological circumstances. In some instances these patterns appear to be highly characteristic of the disease process. The patterns which may be recognized in the future will undoubtedly clarify some of the present day little understood or unknown leukocyte functions. At present, however, he states, the investigation of leukocytic metabolism is largely in the descriptive phase. For the present and until further facts are known, the remainder must be considered as largely speculative in nature.

A study of the concentration of folic acid in leukocytes of normal subjects and patients with leukemia has been made by Swendseid, Bethell and Bird (90). They found that the folic acid content in these cells was greater in patients with leukemia and that this increase could be correlated with cell immaturity, the highest leukocyte folic acid values being noted in the acute forms of the disease. The predominant form of folic acid in the leukocyte was shown to be folinic acid.

The Polymorphonuclear Leukocytes—Origin and Staining Characteristics.—An excellent summary of the functions of the neutrophils and other white blood cells with a bibliography of over 200 articles has been written by Rebuck (88). The main characteristics of these cells are briefly stated by Bunting (91) as follows: It is "a differentiated end-cell without power of reproduction, characterized by an eccentric horseshoe shaped or S shaped lobed nucleus and by the specific fine granulations of the cytoplasm. Functionally it is marked by the extremely active ameboid motion and by the power of phagocytosis. It also furnishes a proteolytic enzyme and may play a part in the coagulation of the blood." This cell is one of the most distinctive of the body both in its specific function of combating infection of various types and in its appearance and origin. In health it is derived solely from the myelocytes of the bone marrow in adult life. When fully developed the cell has an average diameter of approximately 10 microns with variations from 9 to 12 microns. The cytoplasm is uniform in character with the exception that it contains large numbers of extremely minute granules which with Wright's stain have a faint pink or violet pink color. The cytoplasm in young cells has a faint basophilic reaction but in the older cells it is slightly but definitely acidophilic and hence has a faint pinkish tint. The nucleus is made up of coarse chromatin strands which stain a deep

that the true proportion of these cells is somewhere between 63.6 and 76.4 per cent.

✓**Quantitative Biochemical Studies on Leukocytes.**—In recent years a special study has been in progress dealing with the various metabolic changes which occur in leukocytes. An admirable review of the progress in this field has been published by Valentine (80). Many of the statements made below are derived from this source. Such studies are possible mainly through two types of investigation, namely, 1, selective histochemical localization of biochemical constituents and enzyme activity, and 2, by quantitative estimations of biochemical constituents and enzyme activity by an in vitro study of whole blood or separated leukocytes.

It has been shown that the leukocytes consume oxygen (81) and that they produce lactic acid from glucose (82). Investigations have demonstrated, however, that the oxygen consumption of granulocytes is sligtly higher than lymphocytes and the glycolytic ability of granulocytes is twice that of lymphocytes. It has been demonstrated by Wagner (83) that the granulocytic cells from the myelocyte on are apparently the only cells in the circulating blood which have the capacity to carry glycogen and that the glycogen content of blood was markedly increased in myelogenous leukemia and very low in lymphatic leukemia.

Histamine or a histamine-like substance has been identified in the peripheral blood and is known to be present exclusively in the cellular content of the blood and almost entirely in the myeloid leukocytes (84, 85). In chronic myeloid leukemia as much as 250 times the normal amount of histamine is present in the circulating blood. Blast cells, lymphocytes, and eosinophils seem to have little or no histamine. The precise role of histamine in the granulocytes is not known.

The literature dealing with the sulfhydryl content of leukocytes and the possible role of the SH groups in cell division has been reviewed by Contopoulis and Anderson (86). There were high cellular sulfhydryl components in a patient with acute lymphatic leukemia, somewhat less in a patient with chronic lymphatic leukemia, and an amount below the normal range in a subject with granulopenic aplastic anemia.

It is stated by Valentine (80) that many enzymes have been found in the circulating leukocytes including amylase, lysozyme, lipase, proteolytic ferments, catalase, nucleotidase, phosphatase, and B glucuronidase. The subject has been reviewed by Barnes (87) and by Rebuck (88). It has been found that in patients with a leukocytosis the alkaline phosphatase activity of the blood is five times greater than in normal persons. On the other hand, the values in patients with chronic myeloid leukemia with one exception were below normal. Low values were also observed in chronic lymphatic and blast leukemia, but the phosphatase content was high in agnogenic myeloid metaplasia of the spleen.

example this is shown by a patient with Feltys syndrome whom I have had under my observation for several years In this condition there is evidence of rheumatoid arthritis an enlarged spleen and a pronounced leukopenia The total white blood cell count in this patient was as low as 600 per cubic millimeter and the percentage of neutrophils was about 50 at times This would give an absolute number of 300 neutrophils per cubic millimeter as compared to a normal number of about 4800 per cubic millimeter Although this striking leukopenia prevailed for many weeks the patient was ambulatory and did not manifest any evidence of infection nor did she have any complaints except those referable to chronic joint condition

Such a condition as this raises two questions First is the number of circulating neutrophils a completely reliable index of the defense capacity of the body against infection? In this connection it must be remembered that it is the number of neutrophils in the *tissues* which determines the efficiency of the resistance against bacterial infection Second what other circulating cellular elements also assist in the fight against infecting agents? It is known for example that the monocytes likewise function to some extent in this manner especially against certain types of chronic infection such as tuberculosis

It has long been recognized that the neutrophils form a proteolytic enzyme which is especially active in an alkaline medium This enzyme has the capacity to digest necrotic cells and tissues throughout the body which have been injured It is by means of this agent also that inflammatory exudates such as that which occurs in pneumonia are autolyzed and hence the first step made in their removal from the body

Length of Life of the Polymorphonuclear Leukocyte—There is no positive proof of the belief but the indications are that the mature polymorphonuclear leukocyte survives in the circulating blood for a relatively short period of time In patients with agranulocytosis Roberts and Kracke (94) observed that the neutrophils may be entirely gone from the circulating blood within four days after their number begins to diminish Weiskotten (95) has shown that they disappear from the circulation in from three to four days following injury to the marrow with benzol Evidence from the experiments of Sabin Cunningham Doan and Kindwall (96) suggest that one fifth of all the neutrophils are destroyed in 24 hours and hence would indicate a length of life of five days It is entirely possible however that the normal period of survival may be only 10 to 12 hours According to Bunting (91) the chief method of disposal of these cells is undoubtedly removal by the reticulo endothelial cells of the two great blood filters the spleen and the liver

The Immature Forms of Myeloid Cells—Myeloblast—This immature cell gives rise to the myelocyte and mature polymorphonuclear leukocyte

purple, and are sharply differentiated from the surrounding cytoplasm The nucleus of a normal polymorphonuclear leukocyte is distinct from that of any other cell in the body for it is polymorphous and usually consists of from three to five lobes joined by a thin strand of chromatin Since 1904 when Arneth (92) introduced his method of enumerating the different classes of neutrophils by the number of lobes they contained an interest has been maintained in the clinical significance of the so called Arneth count For a consideration of the clinical significance of these changes reference should be made to page 723 where this subject is fully discussed

Of special interest is the motility of the cell with which is associated its most important function of ingesting and destroying bacteria It is the most actively ameboid cell in the body When viewed in the warm stage the cells are usually seen to be undergoing changes in shape constantly by the projection of blunt tongue like protrusions of pseudopodia The rate of speed of these cells has been estimated to be 36 66 microns per minute at 37 degrees centigrade with the limits varying from 53 9 to 30 8 microns per minute (93)

Function of the Polymorphonuclear Leukocyte—At the present time there is no evidence to indicate that this cell has a normal physiological function It is recognized however that it does have the highly important capacity to ingest and destroy certain bacteria and other invading pathogenic agents such as fungi spirochetes viruses and parasites In the protection of the body against such causes of disease, the neutrophils constitute the first line of defense Their method of operation is phagocytosis with intracellular destruction of the infecting organism When areas of the body in which bacteria have invaded are studied under the microscope this mechanism may be seen in operation for it is often possible to observe from 15 to 20 bacteria engulfed in a single neutrophil

The importance of this method of preventing invasion of the body with pathogenic organism is well illustrated in the disease agranulocytosis In this condition as a result possibly of the action of some allergin or toxin in the body there is a maturation arrest of the progenitors of the neutrophils and consequently the mature white blood cells in the bone marrow are not released into the circulating blood Consequently the white blood cell count and especially the percentage of neutrophils decreases until these cells may be entirely absent from the circulating blood With this the first line of defense in the body is no longer effective and the pathogenic organisms which normally are present on the mucous surfaces of the body then invade the body tissues which is sometimes followed by septicemia and death Often with the return of these cells to normal numbers the infection is overcome and recovery results

It is undoubtedly true however that the neutrophils are not the only cells which participate in the defense of the body against infection For

therefore it is impossible to differentiate in some instances between the primitive types of cells especially when a great majority or almost all which are present in the circulating blood are immature

Myelocytes and Promyelocytes —These cells may be defined as those in the stage following that of the myeloblast in which the nucleus is round and granules are present in the cytoplasm It is useful to classify all myelocytes into the three following groups as suggested by Sabin

1 The first stage in which there are not more than 10 granules
2 The second stage in which there are a moderate number of granules
3 The stage in which the maximum number of granules are present in the cytoplasm

The first two types are termed promyelocytes and the third the fully developed myelocyte or differentiated myelocyte because at this period in the development of the cell the granules assume the neutrophilic, baso philic or eosinophilic staining characteristics The presence of promyelo cytes always suggests the possibility that myeloblasts may also be found when the blood is examined with great care

Metamyelocytes —As the neutrophilic leukocyte becomes more mature the nucleus changes from the round to the slightly indented form and then to the shape suggesting that of a horseshoe These are called meta myelocytes With further development the central portion becomes reduced in size to a small thread like connection between the two ends of the nucleus which constitute the lobes The theory of Arneth (*99*) which is based on the idea that as the neutrophil increases in age there is a greater number of lobes to the nucleus has received widespread clinical acceptance It is not however accepted at the present time by Bunting (*100*)

Macropolycyte —This cell is a large polymorphonuclear leukocyte which varies in size from 14 to 18 microns and contains from six to eight lobes to the nucleus It is rarely if ever observed in the blood in health and is seen with greatest frequency in the blood of patients with perni cious anemia It is not however a specific diagnostic finding in this con dition but the presence of these cells in the circulating blood should al ways suggest the possibility that this condition is present

Clinical Significance of Changes in the White Blood Cell Count of the Circulating Blood —The term leukocytosis is used in clinical medicine to describe a total white blood cell count which is above the upper nor mal limit of 10 000 cells per cubic millimeter As the term is used it usually implies that the increase is associated with a change in the number of polymorphonuclear leukocytes Strictly speaking however a leukocy tosis means an increase in the white blood cell count above the com monly accepted limits of normal which might be due to a greater number of any one of the varieties of white blood cells encountered in the blood

Downey (97) supports the view of Naegeli that the megakaryocytes the nucleated red blood cells and the monocytes are also derived from the myeloblasts. According to Downey (98) a cell which is morphologically identical with the myeloblast also serves as a stem cell for lymphocytes in many cases of acute and rare cases of chronic lymphatic leukemia. A majority of clinical hematologists, however are inclined to use the term myeloblast in the more restricted sense to indicate a cell of the most primitive type which gives rise to the myelocyte and mature polymorphonuclear leukocyte

The myeloblast is described as a cell which averages about the same size as the largest lymphocyte of the circulating blood. Some may be comparable to the smallest lymphocytes however, and the largest have approximately the same dimensions as the large mononuclear. The diameter of the myeloblast therefore would vary from 10 to 18 microns. The nucleus is quite large and is round or oval in shape and there is relatively little cytoplasm. It is most frequently made up of chromatin in the form of fine stippling which produces a uniform effect although in some cases it may appear as delicate strands which give a sieve like appearance. *In some cases the chromatin is aggregated about the nucleoli.* The latter number from two to five and with Wright's stain appear as sky blue round areas without a distinct membrane. The cytoplasm is usually deeply basophilic often staining darker than the nucleus and does not contain granules. By arbitrary rule a majority of clinical hematologists classify a cell as a myelocyte even though it has all of the other characteristics of a myeloblast if only one or more distinct granules are present

There are several varieties of myeloblasts which have been recognized. Rieder cells are those which are characterized by several wide and deep indentations in the nucleus producing a lobulated appearance. Auer bodies are large globules or slender rods which are azurophilic in nature staining red with Wright's stain and are sometimes present in myeloblasts. Turk's "irritation forms" are regarded as myeloblasts but resemble plasma cells although the nucleus is that of the myeloblast

It is exceedingly difficult for the average physician to distinguish a myeloblast from a lymphoblast. Downey concludes (98) that myeloblasts similar to those observed in normal marrow occur in the blood of patients with chronic and acute myelogenous leukemia. There may be atypical forms especially in the acute cases but this is not usually the case. It is also concluded by Downey that cells which are morphologically similar to myeloblasts are observed in the blood of patients who are suffering from lymphatic leukemia especially of the acute and subacute types. He observes that when *these cells are numerous in the lymphatic leukemias* there are also intermediate stages between them and ripe lymphocytes. This in his opinion proves the close relationship between the myeloblasts and the lymphocytes in these cases. In the acute leukemias

tosus disseminata and 3 certain hematological disorders as pernicious anemia aplastic anemia and agranulocytosis

The Level of the Leukocyte Count in Relation to Diagnosis in Clinical Medicine.—Of greatest value from the standpoint of diagnosis is the separation of all acute infections into two large groups namely those which are characterized by a leukocytosis and those in which there is a lack of leukocytosis or a neutropenia Those characterized by a lack of leukocytosis are the ones to be kept in mind, for in general it may be said that all of the others are usually associated with a neutrophilia The important ones in which the white blood cell count is not usually elevated are typhoid and paratyphoid fever tuberculosis brucellosis influenza measles rubella and malaria In virus pneumonia there may be a slight increase in the number of leukocytes at the onset of the disease but usually there is a lack of a leukocytosis In some instances as in tuberculous meningitis and in intestinal perforation in typhoid fever the leukocyte count may be increased

In interpreting the leukocyte count in diagnosis it should be kept in mind that various other important influencing factors may be active I would hesitate to make a diagnosis of typhoid fever in a patient in the presence of a leukocytosis unless there were complications present which might account for this On the other hand although a pneumococcus pneumonia is almost always associated with a definite and often extensive increase in the white blood cell count there may be a leukopenia of considerable extent if the infection is especially virulent and the response of the bone marrow is unsatisfactory

The Relation of a Leukocytosis to Thrombosis and Infarction.—In coronary thrombosis there is usually an increase in the white blood cell count from 12 000 to 20 000 per cubic millimeter or in rare instances even higher in a large percentage of patients with the disease This increase is usually associated with an elevation in the percentage of polymorphonuclear cells to a level varying from 75 to 90 per cent in my experience In the patients whom I have seen the leukocytosis is usually apparent within four to five hours after the onset of the condition and persists for several days to a week or 10 days It is important from several standpoints first because it is of some help in diagnosis as it is one of the most commonly occurring changes associated with this condition and second when considered in association with abdominal pain which may be the outstanding feature of the syndrome it may be interpreted erroneously as evidence of some acute abdominal condition which demands immediate surgery Infarction elsewhere in the body is frequently accompanied by a leukocytosis Third it is of some importance from the standpoint of prognosis

A high white blood cell count especially if maintained for a week or more is given by White (*101*) as indicative of an unfavorable outcome in

Table XXXI

CAUSES OF NEUTROPHILIA

1 Acute infections especially coccal certain bacteria fungi spirochetes viruses and parasites
Localized infections
Certain general infections such as rheumatic fever diphtheria smallpox
Development of complications in diseases usually not associated with neutrophilia
2 Intoxications
Metabolic uremia diabetic acidosis eclampsia gout
Poisoning by chemicals and drugs lead mercury digitalis epinephrine
insect venoms black widow spider
foreign proteins after a preliminary leukopenia
3 Acute hemorrhage
4 Postoperative
5 Non inflammatory conditions such as coronary thrombosis
6 Malignant neoplasms when growing rapidly especially in gastro-intestinal tract liver bone marrow
7 Sudden hemolysis of red corpuscles
8 Physiological in the newborn during labor after strenuous exercise after repeated vomiting convulsions paroxysmal tachycardia
9 Myelocytic leukemia and erythremia

(Wintrobe *Clinical Hematology* Courtesy Lea & Febiger)

either under normal or pathological conditions A better term and one which is more precise but one which is not so commonly used is a neutrophilia This clearly implies that there is an increase in the absolute numbers of polymorphonuclear leukocytes

The term leukopenia is used to indicate that the white blood cell count of the peripheral blood is below 5000 cells per cubic millimeter and it is usually assumed that the decrease is due to a depression in the number of neutrophils A more acceptable and definite term when this is the case would be a neutropenia A determination of the total number of white blood cells and the percentage of the several varieties is of value in clinical medicine solely for the following reasons

1 As an aid in clinical diagnosis mainly in the infections and certain of the blood dyscrasias
2 As a basis for a prognosis in certain infections A list of the causes of neutrophilia and neutropenia is given above in Table XXXI

In general it may be said that 1 the most important cause of a neutrophilia are certain acute infections such as pneumonia and others enumerated in the list given by Wintrobe (37) 2 malignancy especially when a neoplasm is characterized by tissue necrosis 3 infarction in any organ of the body such as that associated with coronary thrombosis and 4 certain blood dyscrasias as leukemia and erythremia

While there are many causes of neutropenia the more important are 1 infections characterized by either a neutropenia or a lack of leukocytosis such as typhoid fever or tuberculosis 2 various diseases of obscure etiology as cirrhosis of the liver Felty s syndrome and lupus erythema

White Blood Cell Count in Pulmonary Tuberculosis—The precise value in the diagnosis and prognosis of the total white blood cell and differential count of tuberculosis has yet to be evaluated on a widespread scale The careful and extensive studies of Medlar and his associates (*106 107 108*) and Muller (*19*) suggest that information of value relating especially to the prognosis might be obtained from a determination of the percentage of the various circulating white blood cells

It is considered by Medlar (*106 108*) that

1 The neutrophil plays the chief role in tuberculosis abscess formation and the extension of tuberculous ulcers
2 The lymphocyte predominates when a tuberculous lesion is healing
3 The mononuclear leukocyte is the chief cell of new tubercle formation
4 The total leukocyte counts by themselves indicate roughly the volume of deranged tissue with which the leukocytes have to cope

According to Crawford (*109*) the evaluation of these four components enables one to determine the status of the tuberculous process and to decide whether the leukocytic picture indicates a non septic or healing process a hyperplastic process with the formation of new tubercles which are not undergoing abscess formation or extension of the tuberculous ulcers It is also stated by Crawford that the definitely unfavorable or septic type of pathological process is indicated when neutrophils are above 65 per cent and the lymphocytes are below 25 per cent If to this unfavorable picture there is also evidence of new tubercle formation as indicated by an increase in the monocytes the process becomes more unfavorable New tubercle formation as suggested by an increase in the monocytes in the absence of abscess formation is more favorable Healing is indicated by an approximation of the percentages of neutrophils and lymphocytes with little or no evidence of new tubercle formation as evidenced by a monocyte percentage of below 10

In the interpretation of the relation of the percentages of the various white blood cells in the circulating blood the greatest stress is placed by Medlar (*108*) on the relation of the percentage of neutrophils to those of lymphocytes This ratio is expressed as follows

$$\textit{Neutrophils : Lymphocytes} \text{ or } \frac{N\%}{L\%}$$

A ratio of 1 1 or less represents healing As this ratio increases it represents a less favorable status of the tuberculous process When N% L% reaches 60% 30% or 2 1 it represents a lesion with the trend toward abscess formation which is overbalancing the tendency to heal Hence it can be said that a ratio of 1 1 is ideal one of 2 1 represents the beginning of a process which is unfavorable and increases to 3 1 or 4 1 represent even more unfavorable pathological processes

patients with coronary artery occlusion It is also his belief that the extent and duration of the leukocytosis gives an indication of the size of the infarcted area In a series of 74 patients reported by Levine and Brown (*102*), only four had a white blood cell count of less than 10 000 per cubic millimeter *According to Hamman (103), the average leukocyte count in* this condition is between 12 000 and 15 000 per cubic millimeter rarely is the count more than 30 000 per cubic millimeter In one patient observed by Levine and Brown (*102*) the white blood cell count was 34 500 Hines (*104*) reports a case in which the leukocyte count exceeded 100,000 per cubic millimeter, for a period of 12 days In a series of cases studied by Goodrich and Smith (*105*) the maximum leukocyte count observed was 25,700 per cubic millimeter These authors state that "This patient died and autopsy showed extensive infarction of the myocardium It is usually assumed that such marked increases in the total white blood cell count *indicate extensive acute myocardial pathological change and therefore* a more serious prognosis and in the main this is borne out by the outcome in such cases It is concluded by Goodrich and Smith (*105*) that the total white blood cell count is increased after coronary occlusion averaging from 13 000 to 18 000 in the first four days They found the average leukocyte count to be slightly higher in the patients who died than in those who recovered The polymorphonuclear count is above normal being somewhat higher in the fatal group than in the recovered group These same observers stated that the nonfilament count was almost twice as high in the fatal cases of coronary occlusion as in the group which recovered *It is their opinion that a nonfilament percentage persisting* above 30 per cent beyond the fourth day of coronary occlusion would suggest a large area of infarction and hence an unfavorable prognosis

Several years ago I observed a female aged 40 years who had an extensive coronary infarction in whom the prognosis appeared to be unfavorable from the onset One striking feature of her case was the greatly increased white blood cell count which was elevated from the time she came under my observation *In the fifth sixth and seventh days of her* illness death occurring on the seventh day the leukocyte counts were 29 000 48 000 and 32 800 per cubic millimeter with 86 90 and 93 per cent neutrophils It should be emphasized that in her case there was also present a thrombosis at the bifurcation of the aorta with gangrene of both extremities

Leukocytosis in Malignancy—A slight leukocytosis is commonly found in patients suffering with malignancy of various types *Usually this is in* the vicinity of 11 000 to 12 000 per cubic millimeter but occasionally it is higher A leukocytosis is not so important in this condition from the standpoint of diagnosis but should be thought of more frequently as a possible explanation of obscure increases in the white blood cell count In some instances it may reach 20 000 per cubic millimeter with a percentage of neutrophils varying from 80 to 90

The earlier view that leukocytosis with an increase in the neutrophils in human tuberculosis is the result of mixed infection is gradually being discarded. Sabin (*110*) observed a leukocytosis associated with a neutrophilia in animals infected experimentally and has shown that a fraction of the tubercle bacillus, namely the polysaccharide, is chemotactic and toxic to the neutrophil. All evidence indicates that in pulmonary tuberculosis, however, the exact number of white blood cells in the circulating blood is unimportant. This is suggested by the knowledge that normal or subnormal counts may be found in both minimal and terminal cases with various types of complications including cavities. The total leukocyte count in tuberculosis, therefore, cannot be interpreted as a reliable index of the patient's condition. The information derived from the differential count is far more reliable.

According to Muller (*19*) no one doubts that a mixed infection may play a part in the increase in the neutrophils of the circulating blood in patients with tuberculosis, but in a majority of cases it is her opinion that such an increase may be ascribed to the tuberculous process as such. It has been stated by Medlar (*106*) that a polymorphonuclear leukocytosis is indicative of abscess formation but a transient increase in these cells is seen in early tuberculosis and in the latent tuberculosis of childhood. It should be emphasized that the tubercle bacillus may cause an inflammatory reaction which is proportional to the virulence of the organism and the degree of resistance of the host.

It is generally believed that the neutrophilic shift to the left becomes greater as the lesions show increasing activity and is progressing and that as the patient improves and the cavity is becoming stabilized, the blood picture tends to return to normal. Although the shift in the neutrophils may sometimes fail from a prognostic standpoint, it is usually of definitive value especially when serial counts are made. As previously emphasized, all evidence indicates that in pulmonary tuberculosis, however, the exact number of white blood cells in the circulating blood is unimportant. This is suggested by the knowledge that normal or subnormal counts may be found in both minimal and terminal cases with various types of complications including cavities. As stated before, the total leukocyte count in tuberculosis, therefore, cannot be interpreted as a reliable index of the patient's condition.

It has been claimed that a monocytosis in patients with tuberculosis is indicative of an extension of the disease, at least a formation of new tubercles. This, however, cannot be accepted too rigidly as applicable to a clinical study of tuberculosis. This is because these cells may show spontaneous fluctuation in their numbers or they may be reduced when there is conclusive clinical evidence that the disease is advancing, and because it is not possible to demonstrate consistently a close correlation of these cells to any definite phase of the disease. As Muller says (*19*), "Whatever

From these figures has been devised the Leukocytic Index (*109*) which takes into account the ratio between the neutrophils and lymphocytes the percentage of monocytes and the value of the abnormal white blood cell count. *A method of calculating this leukocytic index by means of a rotary slide rule, has been devised by Crawford (109)*

Medlar (*107*) is of the opinion that in tuberculosis much of the pathological development because of its indolent nature remains below the level of perception by the now accepted clinico roentgenological methods He believes that it is in this subclinical zone that the leukocytic picture when properly evaluated may become of value Several methods of interpreting leukocyte counts in tuberculosis have been compared by Medlar (*107*) *with respect to their power of differentiating between the* various stages of the disease In his opinion the leukocytic index is the method of choice

In connection with the changes in the white blood cells of the circulating blood the study of the relation of the white blood cells of the body in the formation of the tuberculous lesion as studied by Sabin (*110*) is of interest This fundamental work is of value for many reasons among them being the bearing which it may have on the relationship to the monocytes *of the circulating blood This investigator studied* the biologic effect of purified fractions of the tubercle bacillus such as lipids polysaccharides and proteins in animals In general it was found that every cellular reaction recognized *in the lesions of tuberculosis* can be reproduced by fractions isolated from tubercle bacilli In summary it may be said that the tuberculo lipids and proteins all induce a new formation of monocytes the phosphatide changes monocytes into epithelioid cells and their derivative giant cells the waxes induce the fusion of monocytes into foreign *body giant cells the proteins produce* a more varied stimulation of monocytes such as the formation of epithelioid cells macrophages and both types of giant cells These reactions are least with the soluble and most *with the insoluble forms of these derivatives from the tubercle bacillus* and in every instance they are intensified in tuberculous animals The polysaccharides are chemotactic to neutrophilic leukocytes monocytes are involved only indirectly in that they eventually phagocytose extravasated neutrophilic leukocytes

It is pictured by Sabin (110) that there is a functional unity in the phagocytic mononuclear cells the monocyte macrophage epithelioid cell both types of giant cell and the so called specific endothelial system *Cellular and immunological reactions in tuberculosis* in her opinion center about the monocyte

A few years ago Muller (*19*) published a most comprehensive and authoritative monograph dealing with the changes *in the blood in tuberculosis* The following paragraphs give a condensation of her conclusions in regard to this subject

be a direct proportion between the molarity of the serum and the absolute neutrophil count

Changes in the White Blood Cell Count in Relation to Prognosis —In any given infection a determination of the white blood cell count may give three types of information which is of importance in formulating a prognosis These are as follows 1 the total number of neutrophils may be considered as a measure of the complete response of the bone marrow to any given infection 2 the percentage of young neutrophils is an indication of the effort being made by the bone marrow to combat the infection and 3 the percentage of neutrophils with basophilic granulations in the cytoplasm is an index of the severity of the infection

Total Leukocyte Count —The total number of neutrophils in any given infection is important from the standpoint of prognosis especially if the disease state under consideration is usually associated with a leukocytosis For example if a patient is obviously critically ill with a pneumococcus pneumonia and the white blood cell count is below 6000 per cubic millimeter this in itself indicates a serious outlook If it is apparent from the patient s general condition that the infection is severe and there is evidence that the bone marrow is unable to produce a sufficient number of neutrophils to cope adequately with the situation then this is definite evidence of the ominous outlook

Also in certain diseases which are usually not associated with a leukocytosis the total white count may give some information of value in regard to the prognosis For example in patients with typhoid fever if there is undue depression of the white blood cell count it should be considered unfavorable evidence from a prognostic standpoint Reference to Figure 57 will illustrate this point

Classification of the Various Types of Polymorphonuclear Neutrophilic Leukocytes —The earliest attempt to divide the polymorphonuclear neutrophilic leukocytes into different groups depending on their age was made by Arneth (99) He classified all such cells into five main divisions and furthermore recognized several subdivisions in each one of these five main groups Such an elaborate and complicated classification is entirely unnecessary and hence is rarely employed at present in this country To Arneth however should go the credit of having established the principle which is based on the fact that the nucleus of the neutrophils as it develops from the youngest or myelocyte stage in the bone marrow to the oldest cells of the circulating blood is first round then becomes indented and finally divides into lobes which are connected only by a narrow filament This observer introduced the terms shift to the left" which means an increase in the number of young cells and "shift to the right which indicates that there is an increase in the older cells

The first attempt to modify this complicated procedure was by Schilling (*20 114*) who divided the neutrophils into four groups and introduced

the relationship of the tubercle bacillus and the tuberculous lesion to the monocyte, the clinical phase of the disease is judged much more satisfactorily by the behavior of the *other blood cells*

There is remarkable uniformity of opinion among observers concerning the role of the number of lymphocytes in the peripheral blood in the prognosis of tuberculosis It is generally agreed that the lymphocytes decrease both relatively and absolutely when the disease is advancing and they increase when there is clinical evidence of improvement There is no question in the minds of those who have studied the problem carefully that the behavior of the lymphocytes is prognostically important

On the basis that the monocytes reflect changes in the lesion and the lymphocytes are an index of the resistance of the host, the monocyte lymphocyte ratio has been developed This may be represented by the formula

$$\frac{\text{Total number (or percentage) of monocytes}}{\text{Total number (or percentage) of lymphocytes}}$$

The justification for such a formula in the opinion of Muller (19) lies in the convenience of expressing two variables with one symbol or figure It is her opinion however, that the information derived from the lymphocyte count alone is so much more reliable and hence it does not seem justifiable to obscure the accurate information thus obtained by the uncertainty of the data derived from the monocyte Or as she states it is inadvisable to obscure its (the lymphocyte) importance by calculating the ratio of this apparently sensitive cell to another which is less than one half as sensitive clinically to tuberculous disease

It has been noted for many years that there is a tendency to an eosinophilia in patients with tuberculosis who are doing well from a clinical standpoint As a result many of the early observers considered that it is difficult to correlate the number of eosinophils with clinical activity of the disease

Leukocytosis in Diabetic Acidosis—A leukocytosis is commonly observed in diabetic coma which is independent of any associated infection The white blood cell count usually varies between 18 000 to 19 000 per per cubic millimeter although Root has recorded one of 92 000 (111) and Anderson one of 97 000 per cubic millimeter (112) In some instances there may be a leukemoid reaction As extracellular tonicity in the blood serum appeared to be proportional to the level of the polymorphonuclear leukocytosis in animals it has been suggested by Tullis (113) that this condition might be an important factor in the causation of the leukocytosis observed in diabetic coma He states that the hypertonicity of the serum in this condition is due to an increase in the organic constituents of the plasma, namely sugar urea and ketone bodies He reported observation in eight patients with diabetic coma in which there appeared to

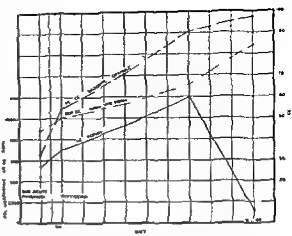

Fig 56—Changes in the white blood cells which illustrate an inadequate bone marrow response to an overwhelming infection The increase in the number of neutrophils containing basophilic granulations indicates the progressive toxicity of the infecting agent Despite the effort on the part of the neutrophils to increase the number of these cells as shown by the increasing number of immature neutrophils the total white blood cell count decreased which is evidence that the total response of the bone marrow against the infection had failed (Bethell courtesy *Journal of Laboratory and Clinical Medicine*)

cytoplasm of the neutrophils was first described by German investigators (*115 116 117 118*) Basophilic granulations or toxic granules as these are designated are taken to indicate the presence of infection in the body The percentage of neutrophils having such granules in the cytoplasm is an index of the severity of the infection in any given patient The clinical significance of basophilic granulations in the neutrophils has been discussed by Rosenthal and his co workers (*119 120 121*) and Sutro (*122*) Basophilic granulations of the neutrophils however, are not limited to the infectious processes but may occur in a wide variety of conditions including reactions following transfusions with incompatible blood in intensive roentgen ray therapy for malignancy or chronic *myelogenous leukemia (123)* As Bethell (*123*) has emphasized these granules are not merely the result of exposure of the neutrophils to a site of inflammation but as they are present in young neutrophils just released to the circulation it is likely that the change in the granules occurs in the bone marrow

Often in association with the changes in the granules other evidences of degeneration in the cytoplasm are found such as bluish staining areas or vacuolization which have the same clinical significance as basophilic granulations By the enumeration of the neutrophils which contain toxic granulations and other evidences of degenerative changes indicative of toxicity and expressing the result in percentage a useful index of the intensity of any given infection which may be compared from day to day is made available

For the purposes of illustrating these changes just discussed the hypothetical case of a patient with a pneumococcus pneumonia may be considered If the white blood cell count is 20 000 per cubic millimeter and neutrophils comprise 85 per cent of these this should be interpreted

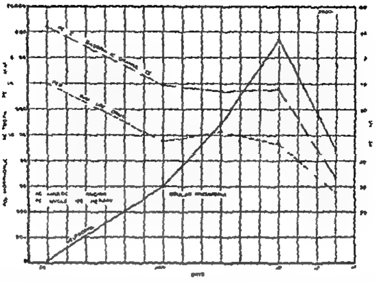

Fig 55—Changes in the neutrophils of the circulating blood of a patient who recovered from agranulocytic angina. Although there was an almost complete absence of neutrophils in the blood when the patient was first observed, favorable evidence was apparent from the subsequent changes in these cells. The percentage containing basophilic granulations became progressively less, the number of young cells was maintained, and there was a steady rise in the total number of the neutrophils of the circulating blood. The high percentage of immature forms in spite of the neutropenia suggested that the bone marrow was at least capable of making an effort to respond. (Bethell, courtesy *Journal of Laboratory and Clinical Medicine*.)

the terms "regenerative shift" which indicated the increase in the younger forms of these cells, and "degenerative shift to the left" which implied a failure of the neutrophils to mature as a result of a depression of bone marrow function. This and other complicated formulas are, in my opinion, unnecessarily complex. The information which one desires to know concerning the types of neutrophils in the circulating blood, is the per cent of young neutrophils which are present. This may be used as a measure of the effort being made by these cells in response to a given stimulus which is usually an infection. The presence of an increased number of young polymorphonuclear cells therefore is indicative of an increased *formation* of young cells by the bone marrow and in addition to other information shows that a leukocytosis is not due merely to the redistribution of white blood cells in the vascular system.

The simplest and most practical method to obtain this information is to divide all neutrophils into the segmented and non-segmented types, which in other words classifies them into the juvenile and older forms. The non-segmented or nonfilamented cells are easily identified because there is no division into lobes with a slender connecting filament. Normally the juvenile or non-segmented forms are present in a percentage of three to five.

Qualitative Changes in the Cytoplasm of the Neutrophils.—The presence of coarse, dark blue irregularly shaped granules throughout the

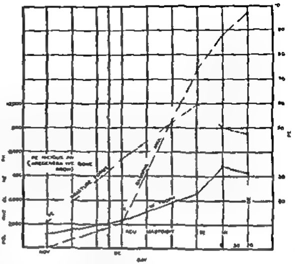

Fig 58 — Unfavorable reaction of the neutrophils to a severe infection in a patient with pernicious anemia terminating in death The ominous signs are the striking rise in the *percentage of cells showing the basophilic granulations* indicating an increase in the severity of the toxemia and the inadequate response of the total number of neutrophils despite the satisfactory effort as shown by the percentage of immature forms This illustrates the fact that in some patients with pernicious anemia the bone marrow reaction may be inhibited by the infection When this occurs the marrow remains functionally incapable of reacting adequately to the infective process (Bethell courtesy *Journal of Laboratory and Clinical Medicine*)

infection in a patient with pernicious anemia who developed an acute infection This chart illustrates another point in relation to the response of the bone marrow namely it is governed to some extent by the state of the bone marrow itself before the infection occurs For example in a patient with untreated pernicious anemia during relapse an infection will *not* evoke a response in the bone marrow characterized by an increase in the number of neutrophils If a spontaneous remission or one induced by liver therapy should be present however there is an exaggerated response to the infecting agent as characterized by a very great leukocytosis which in this case was over 80 000 per cubic millimeter

Summary of the Clinical Significance of Changes in the Neutrophils — In brief it may be said that three types of information may be derived from the polymorphonuclear neutrophil cells when an infectious process attacks the body The adequacy of the bone marrow response is indicated by the total polymorphonuclear neutrophil count the intensity of the response is measured by the percentage of immature forms and the severity of the infection is evidenced by the percentage of polymorphonuclear neutrophil cells containing basophilic granulations If there is a leukopenia indicating an inadequate response of the marrow to infection and if this is present despite the presence of a considerable number of young (nonfilamented) polymorphonuclear neutrophil cells which is evidence that a strenuous effort is being made to increase the count then the findings indicate a failing bone marrow response to an overwhelming infection If in addition there is a severe infection which is suggested by the percentage of polymorphonuclear neutrophil cells exhibiting basophilic granulations the outlook is still more ominous

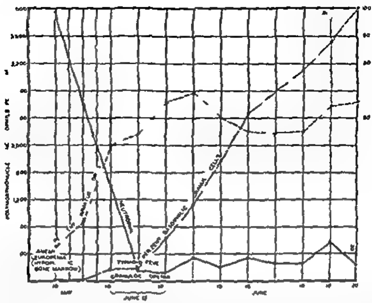

Fig 57 —A fatal case of typhoid fever with extreme neutropenia (130 neutrophils per cubic millimeter) The fatal termination was suggested by the rising percentage of neutrophils in which toxic granules were present and the extreme leukopenia despite the rather high percentage of immature neutrophils which indicated that the marrow was making an intense effort to increase the defense of the body against the infection. (Bethell courtesy *Journal of Laboratory and Clinical Medicine*)

as an excellent response of the bone marrow Furthermore if a per centage of 50 or more of the cells are young as indicated by the presence of a non segmented nucleus it shows that the bone marrow is making a satisfactory effort to produce neutrophils for the purpose of the body's defense Also the presence of basophilic granulations in less than 50 per cent of the neutrophils with a decreasing number each day showing this change denotes that the severity of the infection is not unusual and is becoming less daily All of these signs indicate a satisfactory prognosis from the standpoint of the blood examination If these are associated with clinical evidence of improvement in the patient's condition then the prognosis should be considered as favorable

On the other hand consider the changes in the circulating blood in a patient which would be indicative of an unfavorable prognosis These would be a white blood cell count which was not elevated or was even at the level of a neutropenia that is below 5000 per cubic millimeter with a neutrophil percentage of 50 or less a percentage of non segmented neutrophils of less than 50 with a progressive decrease in the number of these cells each day an increasing number of neutrophils containing basophilic granulations until the number was over 50 per cent or even approached 100 per cent

Figure 56 shows the typical changes in the white blood cells associated with a failing bone marrow response to an overwhelming infection Figure 59 indicates the changes associated with a favorable response to

In dry films stained with Wright's stain the monocyte has a pale grayish blue cytoplasm which usually contains exceedingly fine light staining reddish blue granules Some of the monocytes have granules which can be demonstrated by the peroxidase stain but they are fewer and much smaller than in the granulocytes The nuclei of the mononuclear are of two types the one relatively large and round and the other indented and sometimes resembling a horseshoe in shape Never is the indentation so great however as to give the appearance that the nucleus has two lobes connected by a filament as in the case of the neutrophils The nucleus contains a fine skein like or lacy structure of the chromatin There is no perinuclear clear zone as observed in some of the lymphocytes

A great deal of discussion has been devoted to the origin of the monocyte It has been maintained by various schools that these cells arise from myeloblasts monoblasts from lymphocytes from endothelial cells from active histiocytes from undifferentiated histiocytes or possibly from several sources It is thought by Naegeli Ferrata and by Sabin Doan and Cunningham that the monocyte is derived from the monoblast This cell in turn is considered by some to arise from the histiocytes On the other hand Bloom (*124*) holds the view that the monocytes are neither specific myeloid nor lymphatic tissue cells and that they may have one or several sources of origin He believes the most clearly recognized sources of these cells are the lymphocytes or hemocytoblasts or at least cells which cannot be distinguished from lymphocytes Theoretically monocytes may be derived from fixed reticular cells of either the mature or undifferentiated type It is stoutly maintained by Bloom (*124*) that the idea of the origin of this cell from a specific monoblast that is a free cell morphologically different from a hemocytoblast (i e a myeloblast or lymphocyte) has not been demonstrated and furthermore according to this observer has been proved untenable on the basis of the evidence so far advanced Despite this statement however in my opinion the idea that the monocytes arise from a specific monoblast is the most helpful one for the clinician to assume for the present

Function of the Monocytes —There is no question but what the monocytes bear some relationship to resistance against chronic infection It has not been demonstrated however that they play a role in combating acute infection but this is a possibility Studies have shown that these cells have the power of phagocytosis and it is known that they are capable under certain conditions of developing into macrophages and fibroblasts

They undoubtedly play an important role in the formation of the tubercle as it has been shown by Sabin (*110*) that the lipoids of the organism are phagocytosized by this cell which causes their partial degradation and resultant transformation into epithelioid cells This activity

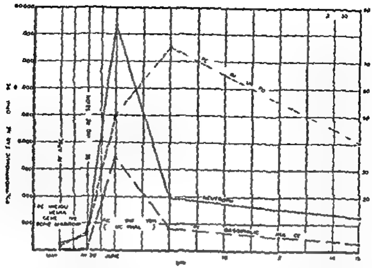

Fig 59 —Patient with pernicious anemia who developed a severe infection which was thought to be an acute encephalitis With the beginning of the therapeutically induced remission and the simultaneous onset of the infection there was an extraordinary neutrophil response as indicated by a total count of 83 000 per cubic millimeter It is known that the leukopenia of pernicious anemia and the high percentage of segmented forms (shift to the right) which is present during relapse is replaced by a normal neutrophilic picture when potent antipernicious anemia medication is administered *If an infection develops at the time of the reticulocyte response there may occur an* unusual neutrophil response as shown by the blood changes in this patient It appears in such patients that the bone marrow is hyperactive and supersensitive and hence the stimulus of even a moderate infection produces a maximal response (Bethell courtesy *Journal of Laboratory and Clinical Medicine*)

On the other hand favorable bone marrow activity in the presence of an infection, is indicated by an adequate increase in polymorphonuclear neutrophil cells and the presence of a moderate increment over normal of the nonfilamented polymorphonuclear neutrophil cells When this information is considered with the fact that only a few contain basophilic granulations the prognosis in so far as it can be determined by the morphologic changes in the blood is favorable

The Monocytes—Structure and Staining Characteristics—The monocytes number between 3 and 5 per cent of all the circulating white blood cells They are somewhat larger than the lymphocytes being about the same size as the eosinophils as they measure from 12 to 20 microns in the usual dry smears In the spherical state however these cells are smaller measuring 12 to 14 microns in diameter Ordinarily there is no difficulty in differentiating between the monocytes and the lymphocytes of the circulating blood It must be admitted however that in almost every blood film there are cells which are called intermediate forms having some of the characteristics of both monocytes and lymphocytes In clinical medicine when doubt exists as to whether a cell is a monocyte or lymphocyte it is generally more accurate to classify it as the latter Those who claim that the monocyte has its origin from the lymphocyte place great stress on the presence of these indeterminate cells as indicating such a transition

in clinical medicine to classify the large lymphocytes as young and the small lymphocytes as older cells

The Function of the Lymphocyte—It is stated by Maximow (*125*) that "there seems to be no secure basis for the discussion of the functions of the lymphocyte" It is not known whether these cells are active in the circulating blood or in the tissue it is usually supposed that their functions are in some way connected with their quantity in the circulation It is known that the lymph nodes are active in combating infection and it is likely that the lymphocyte in some unknown manner contributes to this essential activity of the body There has been considerable speculation concerning the relation of the lymphocytes to various metabolic functions of the body such as the formation of enzymes but these claims have not been substantiated

The development of a lymphocytosis in infectious mononucleosis and pertussis suggests that these cells possess some ability in combating such infections but their exact role is unknown Lymphocytosis is observed in the following conditions

1 In infancy
2 Certain infections as pertussis rubella mumps infectious mononucleosis undulant fever
3 Lymphatic reactions to pyogenic infections in childhood
4 During convalescence from any infection
5 Tuberculosis when resistance is good
6 Exophthalmic goiter
7 Lymphatic leukemia
8 Chronic infectious lymphocytosis (*37*)

The following conditions are associated with a lymphopenia (total number of lymphocytes per cubic millimeter being less than 1000)

1 Acute infections with neutrophilia
2 Advanced Hodgkin s disease
3 Tuberculosis when the resistance is poor
4 Excessive irradiation
5 Agranulocytosis in the advanced stage
6 Leukemia other than lymphatic
7 Subleukemic lymphatic leukemia
8 In conditions of stress such as in acute pancreatitis ruptured duodenal ulcer etc

Lymphopenia in Conditions of Stress—It has been shown by Herfort (*126*) and confirmed by Roberts Baggenstoss and Comfort (*127*) that a lymphopenia of clinical significance occurs in a high percentage of patients with acute pancreatitis This finding has more recently been corroborated by Hirst and Johns (*128*) who found that this disorder was

results in an increase in the monocytes in the circulating blood which is regarded as an unfavorable sign in this type of infection The ratio of the monocytes to the lymphocytes in the circulating blood is thought to be of importance in this disease for the latter vary inversely with the monocytes and an increase in the latter cells is regarded by some as a favorable sign

In subacute bacterial endocarditis it is known that monocytes in the circulating blood may be observed ingesting erythrocytes or even neutrophils This occurs in almost all cases of the disease in the active stages although in some instances such cells may be exceedingly scarce and often will not be found unless a prolonged search is made by an expert observer

In general it may be said that the alterations in the numbers of monocytes are not of great assistance in the diagnosis or prognosis of diseases in clinical medicine This is because the changes in the number of these cells are often relatively small too frequently the differential count is based upon the enumeration of an inadequate number of cells and the inexpert will in some instances confuse monocytes with lymphocytes The list of conditions associated with a monocytosis is as follows

Conditions associated with a monocytosis

1 Chronic infections as brucellosis and subacute bacterial endocarditis
2 Tuberculosis, when condition is advancing
3 Rickettsial disease as typhus and Rocky Mountain spotted fever
4 Hodgkin s disease sometimes
5 Monocytic leukemia
6 Tetrachlorethane poisoning
7 Recovery phase of agranulocytosis

The Lymphocyte—Origin and Description—The lymphocyte is derived from lymphatic tissue in various parts of the body such as lymph glands solitary lymph nodes of the intestines Peyer s patches the thymus tonsils and possibly the bone marrow Two forms occur normally the small variety which measure from 8 to 10 microns and the large cell type which varies from 10 to 20 microns in diameter The small lymphocyte has such a characteristic appearance that it should never be mistaken for any other cell in the blood The nucleus stains a dense deep purple it is round or slightly indented and is surrounded by a small rim of sky blue cytoplasm which in some instances is almost invisible when stained with Wright s stain When lymphocytes are younger the cells are larger (12 to 20 microns) the nucleus is less dense staining and there is a much greater amount of cytoplasm present It has not been shown conclusively that there is a true maturation cycle of the lymphocytes as in the case of the myeloid cells but it has long been customary

neutrophils Many are about the same size as the neutrophils although in some instances they may be larger The nucleus of the eosinophils is usually bilobed although three or more lobes may be observed in the blood of patients with pernicious anemia The cell body is crowded with relatively large granules which have an affinity for the acid dyes and hence stain red with Wright's stain In some instances if this stain does not have the proper neutral reaction the granules of the neutrophils may assume a reddish appearance and be confused by the novice with the true eosinophilic granules This mistake would be made only by the inexperienced as the granules in the two types of cells should be distinguished on the basis of size alone for the eosinophil granules are much larger

The exact function of the eosinophil is not known although it is considered that it may have to a certain extent the capacity to ingest and destroy pathogenic bacteria It is not however considered to be primarily a phagocytic cell for bacteria or cell products There is acceptable evidence to indicate that it is related in some way to defense against animal parasites The increase in various allergic conditions at once suggests their importance in such conditions but this relationship at present is obscure Bunting (*135*) concludes his articles in the Granular Leukocytes in the volume on *Special Cytology* edited by Cowdry by stating The function or functions of the cell and its exact life history must be left as a matter of uncertainty at the present time

In a recent study Vaughan (*136*) has concluded that after being formed in the bone marrow the eosinophil probably travels via the blood stream to the lungs or intestines where it leaves the blood stream and proceeds to the mucosa of the bronchus or intestine Here at least in the lung it either passes through into the lumen of the bronchus and is so eliminated from the body or is taken up by the lymphatic system whereby it may re enter the blood stream from which it is extracted by the spleen and destroyed It is the belief of this observer that in all probability the function of the eosinophil is to carry histamine or a histamine like toxic material from the bone marrow to the tissues for inactivation According to this author this concept of the function of the eosinophil supplies a common factor which can be applied to the widely different clinical conditions with which eosinophilia is associated in man It also provides an explanation of the clinical syndrome characterized by an eosinophilic infiltration of the lungs (Loffler's syndrome)

The Normal Number of Eosinophils in the Circulating Blood—With the demonstrated increased importance of the relationship between the adrenal cortex and the number of circulating eosinophils it has become necessary to evaluate the standards for the normal eosinophil count and the physiological variation of this relationship to form the basis for various functional tests

associated with a lymphopenia below 10 per cent of the total white blood cell count in 55 per cent of the patients with this disorder This reduction in the number of lymphocytes was not limited to acute pancreatitis because it was also present to this degree in 66 per cent of the cases of arteriosclerotic abdominal aneurysm with rupture, in 42 per cent of the patients with acute appendicitis in 37 per cent with dissecting aneurysm in 41 per cent with intestinal obstruction in 40 per cent with perforated duodenal ulcer The lymphopenia is not merely a reciprocal relationship with a polymorphonuclear leukocytosis Hirst and Johns (*128*) believe the condition results from stress whether it is due to trauma intoxication, or infection and the degree of lymphopenia is directly proportional to the extent of the stress The mechanism it is believed, is the one emphasized by Selye (*129*) namely stimulation of the adrenal cortex by the pituitary adrenotrophic hormone with the liberation of adrenal cortical steroids which are active in producing the lymphopenia

Bilobed Nuclei in Lymphocytes Following Exposure to Radiation—Of great interest is the observation that exposure to irradiation even in small amounts may produce an increased incidence of bilobed lymphocytes This alteration was first reported in 1949 by Ingram and Barnes (*130*) and was based on studies of cyclotron personnel at the University of Rochester A later report was published in 1952 (*131*) Although bilobed lymphocytes may appear in other conditions such as infectious processes and leukemia nevertheless their detection is of value in the prevention of radiation injuries This is because 1, the increased incidence of binucleate lymphocytes probably results from exposure to small amounts of radiation and 2 lymphocytes for examination may be obtained with great ease by the usual technic of blood examination It is of interest to note that an occasional lymphocyte of this type has been observed in irradiated animals (*132 133*) According to Ingram and his associates unpublished reports indicate that they have been observed in radiation workers in other institutions

Removal of Lymphocytes from Circulation—It has been shown by Weisberger and his associates (*134*) that in rats the intravascular injection of lymphocytes obtained from the lymphatic system fails to increase the number of circulating lymphocytes This results from the selective action of the lungs in removing these cells after intravenous or intra arterial injection The authors believe that the spleen and possibly the liver and kidneys also play a part in the removal of the transfused lymphocytes but they are not as active as the lungs in this respect These results are similar to those obtained after transfusing granulocytes and suggest that the lungs may act as an important means of controlling the level of the white blood cell count

Eosinophils—Origin, Structure and Function—These cells are derived from the myeloblasts and pass through the myelocyte stages as do the

apparently stimulates the hypothalamus or hypophysis and thus affects the adrenal cortex secondarily Cortisone also produces an eosinopenia by acting directly on the unknown mechanism which regulates the numbers of eosinophils in the circulating blood

As suggested by Thorn and his associates (*147*) the measurement of the decrease in the number of circulating eosinophils four hours after the injection of ACTH or small doses of epinephrine subcutaneously forms the basis for a *clinical test* of adrenocortical and pituitary adreno cortical reserves respectively In a more recent article (*143*) Roche Thorn and Hills suggest that the measurement of the decrease in the number of circulating eosinophils four hours after the injection of 25 milligrams of ACTH or 0 3 milligram of epinephrine before a surgical operation is an acceptable index of the ability of the adrenal cortex to produce 11 oxysteroids and furnishes a good basis for a preoperative prognosis A drop of 50 per cent or more from the initial level is con sidered to be a normal response

Such a functional test is useful in the diagnosis of Addison s disease and panhypopituitarism (Simmonds s Disease) for if there is an eosino penia following the injection of ACTH it would cast doubt on the diag nosis of Addison s disease and if there is such a change in the eosinophils following the injection of epinephrine it would suggest that the anterior pituitary gland is intact

Failure to obtain an adequate eosinopenic response may be due to any one of the following reasons as pointed out by Best and Samter (*145*) 1 inaccuracies of the test resulting from chance and physiologic varia tions 2 refractoriness to a single dose of ACTH ephedrine, or epineph rine which may be due to unknown causes and this has been observed in other conditions than Addison s disease (some link in the chain other than a deficient adrenal cortex might be responsible for the failure to respond) and 3 the patient might during the test be receiving stimuli resulting in a release of adrenocortical hormones and the relatively slight stimulation of the test may then be insufficient to induce further eosino- penia Thus a negative test would result in a patient who at other times would have a positive test

It appears likely that a positive test supplying negative evidence is more reliable than the reverse That is an eosinopenia following the injection of one of the test materials is more reliable evidence against the diagnosis of Addison s disease than a failure to produce an eosino penia is in proving the presence of this disease

Eosinophilia in Clinical Medicine—Regardless of the obscurity con cerning the origin and function of the eosinophil an eosinophilia is of considerable diagnostic value in clinical medicine The presence of an outspoken eosinophilia in a patient that is one exceeding 3 per cent or an absolute number greater than 300 per cubic millimeter should at once

It is obviously inaccurate to express the number of eosinophils in the circulating blood as a percentage of the total leukocyte count. The present day accepted method of stating the number of such cells is to give the actual number per cubic millimeter. This figure has been given as 0 to 400 by Osgood (*137*), 50 to 400 by Todd and Sanford (*138*), 75 to 300 by Kracke and Parker (*139*) and 100 to 250 by Thorn (*140*). More recently it has been suggested by Fisher and Fisher (*141*) that for clinical purposes a normal range of from 25 to 300 per cubic millimeter would seem acceptable.

A modification of Dunger's method for the enumeration of the eosinophils (*142*) is recommended and also a modification (*143*) of the method suggested by Randolph (*144*) has been found to be reliable.

The intrinsic errors of enumeration have been evaluated by Best and Samter (*145*). They conclude that with a total count of 50 per cubic millimeter the error would be ±23, with a count of 100 it is ±33, a count of 200 ±46, a count of 300 ±62. It is therefore fallacious to place too much dependence on a single count when evaluating the various function tests which have a bearing on the integrity of the adrenal cortex. The interpretation should be based upon the curve constructed from a number of counts or on a repetition of the test.

It is pointed out by Best and Samter (*145*) that certain physiological variations occur which should be kept in mind. For example, there are significant minute to minute fluctuations and a more marked diurnal trend with a mid morning low and night time peak. Furthermore tests with ephedrine or epinephrine frequently show significant differences when repeated in the same subject. Moreover many patients with various diseases fail to react adequately to these drugs.

It should be kept in mind therefore that the results of functional tests of the pituitary and adrenal cortex based on changes in the number of eosinophils in the circulating blood as an index of adrenal cortex activity, although useful, should be accepted with caution and only after correlation with the clinical aspects of the patient's condition.

The Response of the Circulating Eosinophils to Various Stimuli.—The level of the circulating eosinophils is influenced significantly by the activity of the adrenal cortex. It is known for example that alarm stimuli in animals is followed by a striking fall in the number of circulating eosinophils (*146*). These blood changes occur because after stress there is a release of adrenocorticotrophic hormone (ACTH) by the hypophysis which in turn stimulates the adrenal cortex. This results in a release of the steroid hormones (11 and 17 oxysteroids) which produce in some unknown manner a reduction in the number of circulating eosinophils (*147*). A similar eosinopenia results from an injection of ACTH which acts directly on the adrenal cortex. The same effect results from the administration of epinephrine or ephedrine which

It has been reported that *following injections of gold* in the treatment of patients with rheumatoid arthritis there may be a constant eosinophilia which reaches levels of over 40 per cent but more frequently it is in the vicinity of 8 to 18 per cent (*150 151 152*) In the publication by Feisner Lapin and Steinbrocker (*152*) it is stated that in 18 patients with arthritis receiving intensive gold therapy eosinophil counts varying from 5 to 45 per cent were observed in all cases As a general rule the patients who received the highest dosage showed a greater eosinophil increase No direct relation between eosinophilia and toxic reactions was observed although one patient who developed exfoliative dermatitis had a maximum increase in eosinophils It is the opinion of the latter authors which is in accord with that of Sundelin (150) that eosinophilia is not a contraindication to further gold therapy since it subsides promptly when the medication is discontinued

Although eosinophilia in uncomplicated chronic intestinal amebiasis is unusual a patient with this condition and an eosinophilia of 15 per cent has been reported by Switzer (*153*) No other cause for the eosinophilia was found and the number of eosinophils fell promptly after the administration of carbarsone The lungs showed no changes in the roentgenogram The author believes that patients who have an eosinophilia of obscure origin should have careful stool examinations by an experienced laboratory worker By so doing in his opinion a greater number of patients with an eosinophilia would be found to have amebiasis as a cause of the condition

Eosinophilia in Tropical Disease —Lowe (*154*) has investigated the blood picture of a large number of Australian soldiers who had been in tropical service for a few months Most of them had suffered from more than one tropical illness usually a combination of malaria and helminth infection Their findings in regard to the number of eosinophils were as follows

	Average Eosinophils Per Cubic Millimeter
Normal control (100)	145
Malaria convalescent (100)	250
Malaria convalescents with Trichocephalus (trichuris)	710
Malaria convalescents with hookworm	1 300
Malaria convalescents with Strongyloides	2 570

It is obvious from the above figures that patients convalescent from malaria but in whom no helminth infestation can be found show some degree of eosinophilia The range in the individual cases which gives the average figure of 250 cells per cubic millimeter was from 0 to 1350 cells per cubic millimeter

The three common helminths which were found in the patients were hookworm Trichocephalus Trichuris and Strongyloides stercoralis The

arouse the suspicion that the patient has a parasitic infestation or allergic condition, although of course such an eosinophilia might be associated with a number of other conditions as indicated below

1 Parasitic infestations especially with trichinella echinococcus and intestinal worms
2 Skin disease of all types including those due to drugs and especially pemphigus and dermatitis herpetiformis
3 Allergic phenomena as allergic rhinitis bronchial asthma urticaria angioneurotic edema and some cases of food allergy
4 Certain unrelated conditions as scarlet fever rheumatoid arthritis periarteritis nodosa Loffler s syndrome dermatomyositis erythema multiforme neoplasms involving serous surfaces or bones
5 *During convalescence from an acute infection accompanied by* neutrophilia
6 Following the ingestion of a liver diet in patients with pernicious anemia
7 Following irradiation
8 As a familial anomaly
9 In some patients with Hodgkin s disease
10 In eosinophilic leukemia

In general it may be stated that an eosinophilia is most commonly observed in trichinosis allergic conditions and in infestations with intestinal parasites It is sometimes helpful in directing attention toward the presence of obscure disease such as periarteritis nodosa in which it is commonly associated and in such rare conditions as dermatomyositis Recently in a patient with the latter condition in whom the diagnosis was confirmed by biopsy (A L B 547798) the eosinophil count was found to be as high as 53 per cent at which time the total white blood cell count was 7000 per cubic millimeter

A patient with *periarteritis nodosa* and a leukocyte count of 60 000 to 100 000 per cubic millimeter with eosinophils varying from 64 to 90 per cent has been reported by Blackburn (*148*) He reviews the literature and from his findings it is suggested that other cases of periarteritis nodosa have been erroneously reported as having eosinophilic leukemia

It is reported by Kauffman (*149*) that an eosinophilia during the acute state of *infectious mononucleosis* is not rare He found in a group of 82 cases that 41 5 per cent had 4 per cent or more of eosinophils and 26 8 per cent had 5 per cent or more frequently in the acute febrile stage In his opinion a blood smear showing numerous atypical mononuclear cells especially with a decrease in the percentage of neutrophils and a shift to the left suggests the diagnosis of infectious mononucleosis and an eosinophilia of 4 to 10 per cent is another point in favor of the diagnosis

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average eosinophil count in 200 cases of hookworm infestation was 1800 per cubic millimeter, with a range of from 0 to 12 500 cells per cubic millimeter In 11 patients in whom there was an infestation with Trichocephalus the range of the eosinophil count was from 240 to 1700 per cubic millimeter These counts are within the range of that for subjects convalescent from malaria and hence Trichocephalus cannot be considered as a frequent cause of significant eosinophilia In all 16 cases of infection with Strongyloides which were studied there was a pronounced eosinophilia In these cases the number of eosinophils numbered from 1100 to 12,600 cells per cubic millimeter the average being 4300 In the opinion of Lowe (*154*) coexistent helminth infestation and malaria infection probably contributed to this rise in the number of eosinophils

Of great interest in the report of Lowe (*154*) is a study of 14 patients with unexplained eosinophilia in whom these cells ranged between 1000 and 3000 cells per cubic millimeter With a total leukocyte count of 10 000 per cubic millimeter this would mean an eosinophilia of between 10 and 30 per cent The presence of an eosinophilia in persons who have lived in the tropics is well recognized and it has usually been assumed that such increases are probably due to the presence of undetected helminths In these patients a careful search was made including cultural examination of the feces for larvae and repeated blood examinations for filaria but in each case these have failed to reveal any parasites except those of malaria As the author states probably correctly, as the eosinophilia in patients convalescent from malaria does not exceed 1750 per cubic millimeter it is thought that some undetected cause is responsible for the greater eosinophilia in these cases All of these patients were treated with anthelmintic drugs without a reduction in the eosinophilia

Under the heading of Tropical Eosinophilia a new disease entity is reported by Parsons Smith (*155*) characterized by severe spasmotic bronchitis leukocytosis and eosinophilia He refers to the previous report of Weingarten (*156*) in which 81 patients with this condition were described In many of the latters patients the condition had persisted for years most of them having been diagnosed and treated as having pulmonary tuberculosis or chronic bronchial asthma It is of course possible that in some of the more acute instances the condition may be an example of Lofflers syndrome It is of interest that arsenic is considered to be a quick acting and specific remedy for the condition As this disease may well be due to several widely separate etiologic agents and there may be a tendency to periods of spontaneous improvement it appears wise to defer an evaluation of such a therapeutic claim to a time when more observers have had an opportunity to determine its effect

It is emphasized by Apley and Grant (*157*) that there are certain similarities between intrinsic asthmas periarteritis nodosa Lofflers syn

drome and tropical eosinophilia All four of these diseases have a chronic course an increase in the number of circulating eosinophils asthmatic symptoms and signs and no obvious etiology It is suggested by them that the difference between tropical eosinophilia and Loffler s syndrome is more apparent than real and it would be more logical to consider them as different manifestations of the same disease process At present the consensus is that tropical eosinophilia is an allergic response to a variety of allergens (*158*) including infestation with animal parasites such as mites amebae or filaria Infestation with these parasites however does not always produce the syndrome

Loffler s Syndrome —This disorder which may be defined as due to transient pulmonary infiltrations associated with an eosinophilia of the circulating blood was first described by Loffler in 1932 (*159*) The condition is usually characterized by attacks of asthma with cough the occurrence of an eosinophilia varying from 10 to 60 per cent with a slight leukocytosis the presence of a mild fever and an elevated sedimentation rate Although physical signs in the lungs may be slight or absent the roentgen rays usually show remarkable pulmonary infiltrations most frequently in the lower lung fields It is characteristic for them to disappear rapidly and not to form cavities An excellent review of the condition is given by Hoff and Hicks (*160*) The allergic nature of the condition was not stressed by Loffler but it is now generally considered to have this basis as the cause of the condition In the case reported by Pirkle and Davin (*161*) there were pulmonary migrations which persisted for six months These in the absence of asthma suggested the possibility of pulmonary tuberculosis which the authors ruled out by careful studies and prolonged observation The eosinophilia in their patient varied from 12 to 33 per cent It is of interest to note that Karan and Singer (*162*) observed five cases of transient pulmonary infiltrations which had erroneously been regarded as due to pulmonary tuberculosis

The classical syndrome is characterized by 1, the transient nature of the condition 2 the roentgen shadow in the lung field which rapidly clears 3 the associated blood eosinophilia and 4 the benign course It is important however to search in each case for the definite cause such as Endamoeba histolytic infestation and in association with other parasites as Fasciola Hepatica and Ascaris Lumbricoides Some have considered that the condition is closely related to Weingarten s syndrome of tropical eosinophilia as described by this observer in 1943 (*163*) although Wise (*164*) is not in accord with this theory In all patients in whom the diagnosis of Loffler s syndrome is considered it is necessary also to eliminate as diagnostic possibilities Hodgkin s disease periarteritis nodosa eosinophilic leukemia and pulmonary tuberculosis In addition it is advisable to follow the patient for a considerable period of time in order to detect some other possible explanation for the patient s findings

A case of Loffler's syndrome associated with pericardial effusion and venous thrombosis has been reported by Dickie and Grimm (*165*). This case was considered to be similar to the ones observed by Harkavy (*166*). It was thought that the various features of the patient's illness were due to a hypersensitivity as there was a history of bronchial asthma, an eosinophilia in the blood (40 per cent), the sputum and the pericardial fluid.

It is emphasized by Fuson (*167*) that a considerable confusion exists in the literature concerning the etiology of the disorder. As many of the patients have bronchial asthma, it is his opinion that the condition is allergic in nature. He also believes that the pulmonary densities are probably due to *atelectases* possibly followed by foci of bronchial pneumonia.

A case of clonorchiasis with a pronounced eosinophilia (65 per cent) in the peripheral blood and bone marrow and bilateral pulmonary infiltrations has been reported by Cartwright (*168*). The similarity and possible relationship of this condition to Loffler's syndrome is discussed.

The *treatment* of Loffler's syndrome is not satisfactory. The mild cases apparently are self limiting. Those associated with bronchial asthma should, of course, receive the proper therapy for the latter condition. In all patients with an allergic background or a stormy course, it is well to keep in mind that the condition might be helped by the administration of epinephrine subcutaneously or aminopterin intravenously. I am not aware at this time that antihistaminic drugs or ACTH or cortisone have been used, but they might be of therapeutic value in severe cases.

Causes of an Eosinopenia.—A review of the literature of the conditions causing an eosinopenia has been given by Hills, Forsham and Finch (*169*). They note that Zappert (*170*) reported a decrease in these cells as a result of a wide variety of infections. The relation of acute infection to eosinopenia is of interest. It has been said that when a neutrophilia occurs, the eosinophils disappear. Some years ago before the relation of the adrenal cortex to the number of circulating eosinophils was known, a physician friend of mine almost succumbed to agranulocytosis following the ingestion of aminopyrine. For six months after recovery there were no eosinophils to be found in his blood even when several thousand cells were examined in cover slip films. Later these cells returned in normal numbers. In view of our present knowledge this probably resulted from a stimulation of the adrenal cortex and release of its steroid hormones.

Others have observed a reduction in the number of eosinophils in animals following injections with turpentine, nuclein, foreign protein, in starvation, exposure to cold, operative procedures, peritonitis, injections of B. coli, sodium bicarbonate or ammonium chloride. In man the reviewers state such diverse influences as the following have caused an eosinopenia: intravascular hemolysis, hemorrhage, hypertensive states,

acute congestive failure ureteral colic and various poisons A reduction in the numbers of circulating eosinophils has been included in the "general adaptation syndrome" by Selye (146) It is the opinion of the reviewers that the adrenal cortex plays an important role in the production of the eosinopenia in the conditions mentioned above in man

In a study of 23 patients with acute myocardial infarction by Feldman Silverberg and Birenbaum (171) however an eosinopenia although present in a majority of patients was not encountered consistently enough to be of differential diagnostic significance Patients were observed occasionally without eosinopenia in the presence of acute myocardial infarction and frequently with eosinopenia in the absence of acute myocardial infarction Nor were these observers able to determine any definite correlation between the degree of the clinical severity and the ultimate prognosis with changes in the circulating eosinophils

It has been found by Altschule Parkhurst and Tillotson (172) that patients who receive electroconvulsive therapy for mental disease exhibit a decrease in the eosinophils of the circulating blood Their findings support the concept that the adrenal cortex is stimulated during such therapy Consequently adrenocorticotrophic hormone is released and exerts its usual effect on the circulating eosinophils Their studies lead them to conclude however that the increased production of 11-oxysteroids considered to be responsible for the eosinophilic cell response is not the cause of favorable results of electroconvulsive therapy

The Basophil.—This cell is somewhat smaller than the average neutrophil, usually measuring between 8 to 10 microns It has a nucleus which is polymorphus or round in shape and takes a rather pale color with Wright's stain It is most commonly composed of three lobes In some instances it is almost obscured by the overlaying granules The most characteristic feature of the cell and the one from which it derives its name is the presence of coarse purplish blue staining granules which are irregular in size Some are larger than those of the eosinophils

The function of these cells has been obscure although as Bunting (100) points out even with a percentage of only between 0 4 to 0 6 it means that there are 200 000 000 of these cells in the circulation which makes one wonder what their purpose might be In 1937 Holmgren and Wilander (173) expressed the opinion that the basophils were responsible for the production of heparin in the body This was the view also held by Jorpes and Bergstrom and further elucidated by them (174) A review of the literature dealing with these cells is given by Janes and McDonald (175)

Never has a percentage or absolute increase in these cells been of any particular assistance to me in the diagnosis of hematological or other disorders except possibly myelogenous leukemia Although these cells may be increased in certain conditions the other clinical manifestations

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Causes of an Eosinopenia.—A review of the literature of the conditions causing an eosinopenia has been given by Hills, Forsham and Finch (*169*). They note that Zappert (*170*) reported a decrease in these *cells as a result of a wide variety of infections. The relation of acute* infection to eosinopenia is of interest. It has been said that when a neutrophilia occurs, the eosinophils disappear. Some years ago, before the relation of the adrenal cortex to the number of circulating eosinophils was known, a physician friend of mine almost succumbed to agranulocytosis following the ingestion of aminopyrine. For six months after recovery there were no eosinophils to be found in his blood even when several thousand cells were examined in cover slip films. Later these cells returned in normal numbers. In view of our present knowledge this probably resulted from a stimulation of the adrenal cortex and release of its steroid hormones.

Others have observed a reduction in the number of eosinophils in animals following injections with turpentine, nuclein, foreign protein, in starvation, exposure to cold, operative procedures, peritonitis, injections of B. coli, sodium bicarbonate or ammonium chloride. In man the reviewers state such diverse influences as the following have caused an eosinopenia: intravascular hemolysis, hemorrhage, hypertensive states,

acute congestive failure ureteral colic and various poisons A reduction in the numbers of circulating eosinophils has been included in the general adaptation syndrome by Selye (*146*) It is the opinion of the reviewers that the adrenal cortex plays an important role in the production of the eosinopenia in the conditions mentioned above in man

In a study of 23 patients with acute myocardial infarction by Feldman Silverberg and Birenbaum (*171*) however an eosinopenia although present in a majority of patients was not encountered consistently enough to be of differential diagnostic significance Patients were observed occasionally without eosinopenia in the presence of acute myocardial infarction and frequently with eosinopenia in the absence of acute myocardial infarction Nor were these observers able to determine any definite correlation between the degree of the clinical severity and the ultimate prognosis with changes in the circulating eosinophils

It has been found by Altschule Parkhurst and Tillotson (*172*) that patients who receive electroconvulsive therapy for mental disease exhibit a decrease in the eosinophils of the circulating blood Their findings support the concept that the adrenal cortex is stimulated during such therapy Consequently adrenocorticotrophic hormone is released and exerts its usual effect on the circulating eosinophils Their studies lead them to conclude however that the increased production of 11 oxy steroids considered to be responsible for the eosinophilic cell response is not the cause of favorable results of electroconvulsive therapy

The Basophil —This cell is somewhat smaller than the average neutrophil usually measuring between 8 to 10 microns It has a nucleus which is polymorphus or round in shape and takes a rather pale color with Wright s stain It is most commonly composed of three lobes In some instances it is almost obscured by the overlaying granules The most characteristic feature of the cell and the one from which it derives its name is the presence of coarse purplish blue staining granules which are irregular in size Some are larger than those of the eosinophils

The function of these cells has been obscure although as Bunting (*100*) points out even with a percentage of only between 0 4 to 0 6 it means that there are 200 000 000 of these cells in the circulation which makes one wonder what their purpose might be In 1937 Holmgren and Wilander (*173*) expressed the opinion that the basophils were responsible for the production of heparin in the body This was the view also held by Jorpes and Bergstrom and further elucidated by them (*174*) A review of the literature dealing with these cells is given by Janes and Mc Donald (*175*)

Never has a percentage or absolute increase in these cells been of any particular assistance to me in the diagnosis of hematological or other disorders except possibly myelogenous leukemia Although these cells may be increased in certain conditions the other clinical manifestations

A case of Loffler's syndrome associated with pericardial effusion and venous thrombosis has been reported by Dickie and Grimm (*165*). This case was considered to be similar to the ones observed by Harkavy (*166*). It was thought that the various features of the patient's illness were due to a hypersensitivity as there was a history of bronchial asthma, an eosinophilia in the blood (40 per cent), the sputum and the pericardial fluid.

It is emphasized by Faison (*167*) that a considerable confusion exists in the literature concerning the etiology of the disorder. As many of the patients have bronchial asthma, it is his opinion that the condition is allergic in nature. He also believes that the pulmonary densities are probably due to *atelectases* possibly followed by foci of bronchial pneumonia.

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The presence of a leukopenia in a patient is often of considerable importance to physicians for several reasons namely 1 it is characteristic of a certain limited number of infections and serves a useful purpose, therefore from a diagnostic standpoint 2 it is indicative of an ominous prognosis in the presence of certain infections which ordinarily evoke a leukocytosis and 3 it is a common feature which serves to segregate a number of important blood diseases.

Leukopenia in Various Blood Dyscrasias.—It should be noted that when leukopenia occurs in various blood diseases it is generally associated sooner or later with an anemia which is usually normocytic or macrocytic in type. The more important anemias in which a leukopenia is constantly present are the subleukemic or aleukemic leukemias of the various types pernicious anemia and aplastic anemia.

As the subleukemic leukemias are classified on the basis that they have a reduction in the number of white blood cells they of course are all included in this group. Certainly the presence of a leukopenia in which 5 per cent or more of the white blood cells are immature forms should at once suggest the possibility that the patient has subleukemic or aleukemic leukemia. Often the diagnosis is further substantiated by the presence of splenomegaly or enlarged lymph nodes or both. Positive confirmatory evidence is usually made available by sternal puncture and the demonstration that there is infiltration of the marrow with leukemic cells. The diagnosis of this type of leukemia is often overlooked and this group of patients is a sizable one among those referred to the Simpson Memorial Institute for observation with the statement that they have a severe anemia of obscure etiology.

The leukopenia of pernicious anemia is discussed fully in the section dealing with this disease. It may be reiterated here however that a leukopenia is one of the most constant diagnostic signs observed in this disease in untreated patients in relapse. When the anemia is well developed that is below 3 0 millions per cubic millimeter a leukopenia is almost always present. Hence if a patient with a severe anemia is thought to have the addisonian variety and is reported to have a leukocytosis it would cast considerable doubt upon the diagnosis but it might be explained by the following circumstances 1 In some instances the nucleated red blood cells are erroneously enumerated

and changes in the blood have been so conspicuous that additional help from a diagnostic standpoint has not been necessary According to Bunting (*100*) the basophils are increased in myelocytic leukemia poly cythemia Hodgkin's disease chronic inflammation of the accessory sinuses and in smallpox and chickenpox He also states that they are found in smears from lymph nodes of patients with Hodgkin's disease, and with eosinophils and other blood cells in smallpox pustules It has been reported that they react (*176*) along with the eosinophils following the injection of foreign proteins into the tissues of animals but the response is somewhat less regular

Plasma Cells —These cells are egg shaped and contain a deep bluish colored cytoplasm when stained with Wright's stain There is often a clear perinuclear zone present The nucleus is eccentrically placed and characteristically *its chromatin is arranged in a pattern resembling the* spokes of a wheel They are considered to be derived from primitive connective tissue cells by some and from lymphocytes by others

Although the plasma cell was first described by Ramon Y Cajal in 1890 there has been little known about it until recent years and even now our knowledge is obviously incomplete although it is thought to be concerned with allergic processes and antibody formation In 1949 Campbell and Good (*177*) concluded that the following facts had been established about these cells 1 it is a cytomorphic variant of a number of cell types of the reticuloendothelial system 2 there is a constant relationship between plasmacytosis and hyperglobulinemia in serum in tissues, and in tissue culture 3 hypersensitivity both experimental and clinical is associated with the development of plasma cells and 4 a cycle of maturation of the plasma cell population is initiated by anaphylactic shock

Rarely are plasma cells observed in the normal blood but occasionally a small number are present in the blood of patients for which no reason can be found It is known however that these cells or cells closely resembling them may be present in numbers varying between 5 and 15 per cent in the blood of some patients with multiple myeloma Also it is recognized that a true plasma cell leukemia may exist For a further description of this condition the section dealing with leukemia should be consulted (page 879) It is also reported that there may be an increase in the number of plasma cells in the blood of patients with rubella scarlatina measles and chickenpox (*178 179*)

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as white blood cells in the hemocytometer, and therefore, an incorrect leukocyte *count reported* 2 *In patients with pernicious* anemia, a leukocytosis may occur at the beginning of a spontaneous or therapeutically induced remission either in the *presence or absence* of an infection As stated elsewhere when a patient with pernicious anemia develops an infection at the time of a remission an exaggerated response with a great increase in the total white blood cell count may occur reaching 50 000 white blood cells or more per cubic millimeter in *some instances* 3 *The presence of a leukocytosis* in a patient thought to have pernicious anemia should always arouse suspicion that the diagnosis is incorrect Such patients may be suffering from some variety of leukemia, a hemolytic anemia or some other form of blood dyscrasia

A leukopenia due to a diminution in the neutrophils is constantly found in patients with true hypoplastic or aplastic anemia This is always associated with a decrease in other elements which arise from the bone *marrow namely the erythrocytes and the blood platelets A leukopenia* is a common accompaniment of Banti s disease Felty s syndrome and Gaucher s disease *It is sometimes seen although not characteristically in Hodgkin s disease and lymphosarcoma In some instances this may be attributed to roentgen ray therapy It is commonly present in lupus erythematosus For example in a recent fatal case of the latter disease* observed by *me* there were 3500 white blood cells per cubic millimeter although 84 per cent were neutrophils

The Mechanism of Production of Leukopenia—Normally the white blood cell count fluctuates between 5000 and 10 000 per cubic millimeter As previously stated it is known that there are certain physiologic variations which are due to age muscular exercise digestive activity and state of nutrition Ordinarily with the exception of the leukocytosis following muscular exertion these variations in the count are within the limits of normal

It is usually assumed that the leukocyte *count reflects the state of* granulopoiesis *in the bone marrow* but this *is not necessarily true* For example the white blood cell count may *be increased or decreased as a result of a redistribution of leukocytes to or from the circulating* blood and areas where they are stored temporarily such as the liver and the lungs and to a lesser extent in other viscera The temporary leukopenia which follows the injection of a foreign protein is known to be due to the sequestration of white *blood cells in the internal organs In* conditions such as agranulocytosis there is an extreme leukopenia in the circulating blood but the bone marrow is found to contain many leukocytes in the immature stage In such a condition the cells are not released to the peripheral blood because they are immature and a condition designating a maturation arrest is said to be present

According to Lawrence *(180)* a leukopenia *may result from* at least four different mechanisms given in the table below

I DIMINISHED PRODUCTION
  1 Inhibition
  2 Maturation arrest
  3 Aplasia of the bone marrow
  4 Infiltration of the bone marrow

II INCREASED LOSS

III ACCELERATED DESTRUCTION

IV REDISTRIBUTION
  1 Retention in internal organs
  2 Between tissues and blood

Although this table lists a number of different processes which result in a leukopenia it is probable that diminished production with its four subdivisions is the most important mechanism Inhibition of development of polymorphonuclear cells without the omission of any of the essential steps in the mechanism of development probably accounts for the leukopenia seen characteristically in typhoid fever and other overwhelming infections from any cause A maturation arrest at the early myelocyte stage occurs in agranulocytic angina Aplasia of the bone marrow accounts for the leukopenia in aplastic anemia Infiltration of the bone marrow with neoplastic cells is not an uncommon cause of leukopenia Redistribution with sequestration of polymorphonuclear cells in the internal organs is responsible for the leukopenia following injections of typhoid vaccine A disturbance of the mechanism which controls the release of polymorphonuclear cells from the site of their formation may be an explanation of the mechanism of the production of leukopenia in some instances of subleukemic leukemia The reader is referred to the article by Lawrence to which reference has been made for a more complete discussion of these processes

Leukopenia in Infections —In any given infectious disease the level of the leukocyte count is determined by a number of factors as follows 1 the nature of the infectious agent 2 the tissue involved 3 the intensity of the process and 4 the state of the bone marrow when it reacts to the infection

The most important infectious diseases which characteristically are *not* accompanied by a leukocytosis are typhoid paratyphoid and undulant fever and uncomplicated tuberculosis certain virus diseases such as influenza measles rubella protozoal infestations as malaria relapsing fever and kala azar In addition various other infectious diseases are also characterized by a leukocyte count below or within normal limits at the onset of the condition which is followed within a few days by a leukocytosis Examples in which this occurs are smallpox virus pneumonia and infectious mononucleosis The knowledge that certain infectious processes are not associated with a leukocytosis throughout the

course of the disease or at the onset is of considerable importance from the standpoint of diagnosis

Brief reference has already been made to leukopenia in the discussion on changes in the leukocytes in relation to diagnosis and prognosis A further discussion for the sake of completeness of this section will be given here

The virulence of the infectious agent is known to play an important role in determining the leukocytic reaction In addition to a leukopenia which invariably accompanies some types of infection a decrease in the leukocytes may sometimes be observed in certain diseases which ordinarily evoke a leukocytosis It is considered that the total number of polymorphonuclear neutrophil cells in the circulating blood is a reliable index of the resistance of an individual to an infection which is ordinarily characterized by a leukocytosis A moderate increase for example in a patient with pneumococcus pneumonia in the white blood cell count to 20 000 per cubic millimeter could be interpreted as a favorable reaction on the part of the body s defense mechanism On the other hand if the leukocyte count was 5000 cells per cubic millimeter or less two interpretations would be possible One that the infection was so mild and trivial that it had failed to stimulate the bone marrow The other that the infection was so intense that the bone marrow was overwhelmed from a functional standpoint and unable to respond As a result the leukocytes had failed to enter the circulation at the regular rate and the total leukocyte count fell When the leukocyte count is definitely in the leukopenic zone that is below 4000 cells per cubic millimeter in a patient with pneumococcus pneumonia, then it must be considered definitely that the organisms are of such virulence that the defense mechanism of the body has been overcome and the outlook therefore is not good

When a leukopenia results from a severe infection it is thought that in some way the causative agent brings about a simple inhibition of the process of development of the leukocytes In other words as previously stated a radical change does not occur in maturation in the sense that any of the steps are omitted The polymorphonuclear neutrophil cells under some unknown specific influence of the infectious agent are merely retarded in their rate of development As normally such cells are not released into the circulating blood until they are mature their emergence into the blood is delayed and consequently a leukopenia results

The site of the main localization of an infection may determine the presence or absence of a leukocytosis For example a leukopenia or a normal white blood cell count is present in association with pulmonary tuberculosis but when the tubercle bacillus affects the meninges there is likely to be a leukocytosis

Only brief reference will be made to the effect of the prior state of the bone marrow when it reacts to an infection The best illustration of this is observed in patients with pernicious anemia who have an anemia of 2 0 red blood cells per cubic millimeter or less As previously stated when such patients develop an infection with a pyogenic organism they do not characteristically react with a leukocytosis unless they are in the initial stages or a fully developed one of spontaneous or therapeutically induced remission At these times they may react with a remarkably high leukocyte count Another example of the effect of the state of the bone marrow in the leukocyte response is in agranulocytosis In such patients even when a profound infection is present there is no leukocyte response because the bone marrow is in a condition of maturation arrest

Collateral information is always available for interpretation of the significance of a leukopenia in any given infection which ordinarily would be accompanied by a leukocytosis The height of the fever the rapidity of the pulse cyanosis delerium and other toxic evidences furnish a reliable index of the intensity of the infection The leukopenia may in some instances forecast the appearance of these signs or when they are present it confirms the clinical impression concerning an ominous prognosis

Splenic Neutropenia —In 1939 Wiseman and Doan (*181*) described a group of cases characterized by a profound neutropenia panhyperplasia of the bone marrow and enlargement of the spleen in which splenectomy was curative As the blood changes were not secondary to any recognizable disease syndrome they designated the condition primary splenic neutropenia The changes in the blood however were not limited to the neutrophils but also included varying degrees and combinations of anemia and thrombocytopenic purpura In each case the anemia associated was of the hemolytic type with an elevated reticulocyte count and slight icterus with a negative direct van den Bergh reaction It was concluded that there could be little doubt but what a single mechanism was responsible for the varying degress of anemia neutropenia and thrombocytopenia and that this mechanism was hypersplenism This view of course was strengthened by the observation that all three formed elements of the circulating blood were increased by splenectomy Additional cases have been reported and the disease discussed by Salzer Ransohoff and Blatt (*182*) Rogers and Hall (*183*) and Muether and his associates (*184*)

The condition was not thought to be Banti s syndrome by Wiseman and Doan (*185*) as there was no evidence of portal cirrhosis or portal hypertension It should not be confused with Felty s syndrome as the joints were not involved Nor did they believe that it was due primarily to infection although this might precipitate the initial symptoms of the disorder Agranulocytosis could be eliminated from consideration as

drug ingestion played no role in the causation of the disorder and the bone marrow changes were not typical of this condition. They cautioned that leukemia of a subleukemic myeloid type may present the most difficult differential diagnosis. Careful blood and bone marrow studies should eliminate subleukemic or aleukemic leukemia as in splenic neutropenia there are never qualitative alterations which are characteristically present in myeloid leukemia.

The diagnosis of splenic neutropenia is epitomized (*185*) as follows: *clinically* there is splenomegaly, occasionally purpura depending on the degree of the associated thrombocytopenia, sometimes oral ulceration which is related to the acuteness and degree of neutropenia, and in some instances a mild icterus which is directly related to the degree of the associated hemolytic anemia. The *bone marrow* shows hyperplasia of the myeloid elements and, if hemolytic anemia is pronounced, of the erythroid series also; there are no abnormal cells present or anything else to suggest the presence of leukemia. The circulating blood shows a striking specific neutropenia and anemia, when present, is macrocytic and normochromic in type (unless some complication exists such as menorrhagia or metrorrhagia); reticulocytosis is observed if there is a definite anemia and an increased indirect van den Bergh reaction is present, the intensity of which is directly related to the grade of anemia; the thrombocytopenia is variable.

The following patient who came under my observation is a typical example of the condition.

A 48 year old female, #681731, had been in comparatively good health until one year previously when she developed ease of fatigue and repeated infections of the eyes and occasionally bouts of what she called the flu. Her local physician found a white blood cell count which varied persistently between 900 and 2000 per cubic millimeter. There was no abnormal tendency to bleed. My examination showed a well developed and nourished woman whose spleen was just palpable at the end of a deep inspiration. There was no enlargement of the lymph glands and the liver was not felt. The blood examination was as follows: hemoglobin 14.5 grams (93 per cent), red blood cell count 5.2 million per cubic millimeter, white blood cell count 700 per cubic millimeter with neutrophils 52 per cent, basophils 2 per cent, eosinophils 2 per cent, large lymphocytes 20 per cent, small lymphocytes 10 per cent, monocytes 6 per cent. The platelets were slightly increased; the reticulocytes less than 1 per cent. The bone marrow as determined by sternal puncture was hyperplastic. Treatment with ACTH and later Cortisone caused only a temporary increase in the white blood cell count to about 3000 to 4000 per cubic millimeter with 50–60 per cent neutrophils. Splenectomy was followed by complete relief of all the patient's symptoms. Ten months after the operation the blood examination was as follows: hemo

globin 13.7 grams (88 per cent), red blood cell count 4.6 per cubic millimeter, white blood cell count 6400 per cubic millimeter with 62 per cent neutrophils. The patient had no complaints at this time.

It is clear, therefore, that there is a syndrome characterized by striking neutropenia and splenomegaly and sometimes an anemia and thrombocytopenia. This condition has been called primary splenic neutropenia by Wiseman and Doan (181). Evidence has been accumulated to indicate that it is due to the basic mechanism of hypersplenism. Cure can be effected by removal of *all splenic tissue* with restoration of all blood cellular elements.

Secondary Splenic Neutropenia.—It has been emphasized by Dameshek and Estren (186) that leukopenia is seen in association with many cases of splenomegaly. For example, it is often observed in infections (typhoid, malaria, tuberculosis, etc.), in infectious-like diseases (rheumatoid arthritis, sarcoid, disseminated lupus erythematosus), portal hypertension (cirrhosis of the liver, portal vein thrombosis, splenic vein thrombosis), lipid disease (Gaucher's disease), neoplasms (benign tumors, Hodgkin's disease, leukemia, lymphosarcoma). In some instances the neutropenia may be extreme and amount to a disappearance of virtually all neutrophils from the peripheral blood. In association with this there is not infrequently a tendency to recurrent mild to severe infections. If such a leukopenia is found in any of the above diseases and there is splenomegaly and also a hyperplastic bone marrow, the condition could then be regarded as a secondary splenic neutropenia. Splenectomy, as in Felty's disease, probably would correct such a condition. This is not necessarily indicated because by removing the spleen the underlying disease process may not be benefited although the blood may return to normal. Hence the sum total of the favorable effects may not be worth while as far as the entire disease picture is concerned. In my opinion the decision for or against splenectomy under these circumstances is often difficult. My own present attitude is a leaning toward the conservative side.

Recurring Acute Infectious Gingivostomatitis with Leukopenia—*Periodic (Cyclic) Neutropenia*.—I have observed two patients with recurrent attacks of acute gingivostomatitis which were accompanied by a remarkable reduction or disappearance of the granulocytes from the peripheral blood for a period of a week to ten days. One patient was a 22 year old female who for two years had suffered from recurrent attacks of painful lesions involving the oral mucous membranes. These episodes are accompanied by fever and a general feeling of malaise. In the interim between the attacks the patient was in apparent good health. When observed toward the end of an attack the white blood cell count was found to be 3800 per cubic millimeter and the differential count was as follows: polymorphonuclear cells 0, large lymphocytes 60 per cent,

small lymphocytes 16 per cent monocytes 23 per cent eosinophils 0 basophils 1 per cent At this time there were superficial ulcerations on the posterior pharyngeal wall, and small aphthous ulcers on the inner aspect of the lower lip One week later, the white blood cell count was 4000 per cubic millimeter and the polymorphonuclear count 22 per cent

Another patient was a 15 year old boy who had suffered from recurring attacks of sore mouth and throat since the age of four years When seen at the beginning of an attack, a small white patch of exudate was observed on the tongue there were superficial ulcerations of the gums and an intense congestion of all the oral mucous membranes At this time the white blood cell count was 4850 per cubic millimeter and the percentage of polymorphonuclear neutrophil cells 45 Three days later the white blood cell count was 2400 per cubic millimeter and only 10 per cent of the cells were of the polymorphonuclear neutrophil type After the oral lesions had been present for four days the body temperature rose to between 101 and 103 degrees (F) for five days and then returned to normal About two weeks after the onset, the total white blood cell count was 8700 per cubic millimeter

A condition in which the mouth lesions are similar has been reported by Scott and his associates *(187)* under the name of 'Acute Infectious Gingivostomatitis In their cases however no blood studies were reported In their opinion the condition observed in their patients was due to the virus of herpes simplex which was isolated from the mouths of patients with the condition Furthermore the patients developed neutralizing antibodies in the blood during convalescence Oral swabbings were made in the case of the 15 year old boy by Dr H E Pearson of the School of Public Health of the University of Michigan during the beginning of an attack and several days later Both of these specimens were inoculated in the scarified cornea of rabbits but in neither instance was a herpes virus recovered Unfortunately neutralization tests using the serum from the patient were unsatisfactory

Although the exact nature of this condition is unknown it is well to remember that a syndrome of possible virus etiology characterized by recurrent attacks of stomatitis fever and striking leukopenia may occur In some instances this may be confused with agranulocytosis

Sixteen cases of the disorder have been collected by Reimann and deBerardinis *(188)* who believe that striking features stand out in the cases They are first that the similarity of the chief manifestations in all cases is sufficient to establish the condition as a clinical entity The second is the remarkable uniform regularity of the cycles at three week intervals In their group the condition usually began in infancy and in 11 of the 16 symptoms appeared before the age of 12 years In two cases however the initial symptoms became evident for the first time at the ages of 56 and 62 years In almost all instances, the episodes when

once they are established have persisted in a cyclic pattern There is however one exception to this statement and that is in one patient the attacks occurred in three distinct periods (189 190) Ten of the 16 patients were males The cause of the condition and the cause for its cyclic nature is obscure according to Reimann and deBerardinis (188) It has been suggested that it may be on a hormonal basis but no proof is available to support this theory In one patient the condition persisted through pregnancy It is likely that the leukopenia is due to changes in the bone marrow

According to the above authors splenectomy is the only form of therapy which might be of benefit A summary of the results in seven cases collected by Reimann and deBerardinis (188) shows that in four patients this procedure produced an amelioration in the symptoms or resulted in less diminution in the neutrophils or both in two cases however no benefit followed In one patient there was a spontaneous disappearance of the symptoms but the neutropenic cycles persisted The treatment of this condition therefore is unsatisfactory and uncertain in its effects Splenectomy should be considered and might be helpful The only other form of therapy indicated is to combat a secondary infection of the oral cavity and elsewhere by the use of antibiotic medication and sulfonamides

In the two instances observed by me the condition has been most persistent In one patient it has been present between the ages of four and 15 years and in the other over a period of two years In the latter patient after the attacks had been established for some time multiple abscesses developed in various parts of the body including the head axillae neck and chest In all probability these occurred because at this time the natural defense mechanism of the body the polymorphonuclear cells had disappeared from the circulating blood Recently this patient wrote stating that two years ago she changed her occupation from that of a dentist s assistant to clerking in a store and had been free from attacks No active treatment has been discovered which was of benefit in either one of these two cases

The Blood Changes in Tuberculous Splenomegaly —The occurrence of tuberculous involvement of the spleen in association with miliary tuberculosis or advanced tuberculosis of other organs is common but extensive active tuberculosis localized in the spleen is rare It is recognized that in the course of tuberculosis of the spleen there are almost always associated changes in the blood forming organs The cause of this mechanism is obscure as indicated in a recent discussion by Engelbreth Holm (191) The blood changes vary widely in nature as there may be anemia polycythemia purpura leukopenia or a normal erythrocyte and leukocyte count

The condition is of special interest to me on account of the pronounced leukopenia which may be associated with it Some years ago a patient

an adult male was observed on my service in whom the white blood cell count was 600 per cubic millimeter and the neutrophil percentage about 48 With this there was fever a moderately enlarged spleen and no other significant changes in the peripheral blood The admission diagnosis was agranulocytosis but as no etiological agent could be established and as the percentage of neutrophils was high and splenomegaly was present, this diagnosis was disregarded in favor of a subleukemic leukemia Support in favor of the latter condition was obtained by means of sternal puncture which showed the presence of large numbers of exceedingly primitive white blood cells This was erroneously interpreted as a maturation arrest The diagnosis was not definitely established until necropsy was performed when it was found that the patient had a widespread miliary tuberculosis with extensive involvement of many organs of the body including the spleen A similar case was seen on my service a few years later

A case of tuberculosis splenomegaly and discussion of this condition in relation to the changes in the circulating blood with references to the literature is published by Brown Mason and Lucia (192) Their patient was a male age 54 who had evidence of chronic infection with intermittent fever the occurrence of petechiae extreme splenomegaly (the spleen weighed 2700 grams at necropsy) moderate hepatomegaly and ascites and a gradually progressive course which terminated in death nine months following the onset of symptoms The red blood cell count and the hemoglobin percentage were both normal throughout his illness but normoblasts were constantly present The outstanding feature of the blood was the pronounced leukopenia with the absolute reduction in the total number of all white blood cells The leukocyte count per cubic millimeter on eight different occasions between November 9 and December 18 was as follows 1350 1500 1100 950 1200 950 1350 1100 The differential formula varied only slightly on each of these occasions A typical differential blood count was as follows neutrophils 66 per cent filament 34 per cent nonfilament 32 per cent lymphocytes 26 per cent monocytes 2 per cent eosinophils 0 basophils 2 per cent normoblasts 2 per cent platelets 140 000 per cubic millimeter On one occasion the reticulocyte count was 12 per cent Sternal bone marrow in this patient obtained by needle puncture revealed a moderate increase in the mature myeloid elements and a slight diminution in the number of red blood cells Material obtained from the spleen showed immature myeloid elements and normoblasts which suggested the presence of hematopoiesis in the spleen

This case along with others reported in the literature indicate that a striking leukopenia without important changes in the other elements of the blood may occur in a patient with extensive tuberculosis involving the spleen In the presence of evidence suggesting a chronic infection

splenomegaly and a leukopenia in which all of the types of white blood cells are reduced but with no change in the number of red blood cells or hemoglobin per cent this diagnosis should be kept in mind

FELTY'S SYNDROME

Synonyms—Chauffard's Disease Still Chauffard's Disease

Definition—A syndrome usually observed in persons of middle age, characterized by the manifestations of chronic rheumatoid arthritis splenomegaly leukopenia lymphadenopathy loss of weight and sometimes cutaneous pigmentation

History—The attention of the present generation of clinicians in the United States was directed to this condition by Felty's description in 1924 (*193*) of a syndrome characterized by arthritis splenomegaly and leukopenia Felty considered that such a condition in adults was comparable to the one described by Still (*194*) in children in 1896 Also in 1896 Chauffard and Ramond (*195*) reported the association in adults of chronic arthritis with enlargement of the lymph glands but no reference is made to an associated splenomegaly Apparently the first mention of the term Still Chauffard's disease was made by Pollitzer (*196*) who regarded this condition as the counterpart of the syndrome now designated as Felty's disease in this country As Singer and Levy state "In subsequent reports by continental writers dealing with the Still syndrome the adult form (Still Chauffard's disease) was sharply separated from the juvenile type" Certain features of the condition had been described separately by others namely Herringham (*197*) in 1909 Giffin (*198*) in 1929 Ward (*199*) in 1923 McCrae (*200*) in 1904 Hench (*201*) in 1933 and Dawson (*202*) in 1935

Etiology—In discussing the etiology of the syndrome Felty states that there are two possible causes 1 "The several features are manifestations of one pathologic process caused by the noxa which simultaneously affects the joints the spleen and the blood leukocytes " 2 "The syndrome is merely the confusion of two separate clinical entities occurring coincidentally in the same individual However on the law of probability alone such a coincidence seems highly unlikely and this rule would violate a fundamental rule of diagnostics—that a symptom complex should if possible be explained on the basis of one pathological process rather than on the assumption of the existence of two or more in short one is more or less forced to the conclusion that this syndrome is a distinct clinical entity of which the outstanding symptoms are those related to the joints and the outstanding signs are the enlarged spleen and the blood picture" Curtis and Pollard (203) agree with Dawson (*202*) that there is no justification for the segregation of these cases and suggest that the use of the term "Felty's Syndrome" be discontinued This viewpoint is based on the belief that the possibility of the combina

tion of the occurrence of splenomegaly arthritis, and leukopenia in the same patient is the result of chance rather than indicative of any specific syndrome

It is my own opinion however that the name "Felty's Syndrome" should continue to be utilized because it indicates a clean cut syndrome first described in this country by Felty, and therefore has a distinct meaning although I am willing to concede that the cause is probably the same unknown etiological agent of rheumatoid arthritis Singer and Levy (*204*) are of the opinion based upon bacteriologic and anatomic evidence in two cases that the cause of the condition is sepsis lenta The usual causative organisms they believe to be a streptococcus of the viridans type, but they consider that it may also be due to other organisms

Pathology—The pathologic changes found in the spleen, the bone marrow lymph glands and the voluntary muscles of the body are those of a chronic infection and are not specific for any special condition The spleen shows changes which are characteristic of a diffuse chronic splenitis The lymph glands are characterized by the pathologic changes of a chronic adenitis due to an infection and in no way do they show specific changes Biopsy of the calf muscle according to Curtis and Pollard (*203*) show alterations which are characteristic of chronic rheumatoid arthritis namely they are the manifestations of a chronic generalized infection as indicated by the following alterations 1 atrophy of the epithelium 2 fibrosis of the corium 3 increase in the interstitial nuclei of the muscle fibers and 4 small perivascular infiltrations throughout the corium and muscle Bone marrow studies on patients with this syndrome shows a cellularity which varies from 60 to 80 per cent Various types of young red blood cells are present

In general it may be said that the pathologic changes encountered in these patients are characteristic of a chronic infection and in no way are they typical of a specific disease process

Symptoms and Physical Signs—The outstanding features of the history and physical examination pertain to 1 the arthritis 2 the spleen 3 the general state of undernutrition and 4 in some cases cutaneous pigmentation The arthritis is of the chronic type and appears to pursue the same course as ordinary rheumatoid arthritis In Felty's cases the duration of the complaints had been on the average four and one half years The onset was either acute or gradual There are the usual generalized and aching pains associated with that disease which are sometimes mild but often severe during periods of acute exacerbation There is not infrequently a loss of 30 to 40 pounds in body weight and hence the patient often appears strikingly undernourished Although Felty thought that the joint involvement was benign in his cases as compared to the usual course of a patient with rheumatoid arthritis this has not been my experience as the general course of the disease in the

two conditions has appeared to be similar A low fever may be present but this does not differ in any way from the febrile reaction commonly observed in patients with rheumatoid arthritis

The splenic enlargement is a classical feature of the syndrome The edge of this organ may be barely palpable or in some cases it may extend 4 or 5 centimeters below the costal margin The edge is firm and non tender It is of interest to note that Hench (*201*) found splenomegaly in about 1 per cent of the cases of rheumatoid arthritis and Dawson (*202*) reported its occurrence in 10 to 15 per cent of the cases The liver is not characteristically increased in size Moderate enlargement of the lymph glands is present in a majority of cases the involvement often being a generalized one Felty described a yellowish brown pigmentation of the skin which in four cases was confined to the exposed surfaces but in the fifth had a wider distribution over the abdomen axillae and flexor surfaces of the arms

Changes in the Blood —There is often a moderate anemia present with a red blood cell count which is usually between 2 5 and 3 5 millions per cubic millimeter and a hemoglobin between 50 and 70 per cent (7 8 to 10 9 grams) The anemia is of the normocytic normochromic type with a color index of about 1 0 and a mean corpuscular volume between 86 and [illegible] cubic microns The mean corpuscular hemoglobin concentration is usually between 30 and 33 per cent and the saturation index from 0 9 to 1 0

The striking feature of the blood is the pronounced and persistent leukopenia as indicated by a white blood cell count which may fluctuate between 600 or 800 to 3500 or 4000 per cubic millimeter The lowest white blood cell count I have observed was one of 650 per cubic millimeter with a differential count as follows polymorphonuclear neutrophils 62 per cent large lymphocytes 12 per cent small lymphocytes 14 per cent monocytes [illegible] per cent eosinophils 6 per cent There may be a reduction in the percentage of neutrophils in the circulating blood below 60 per cent but this is not always present Achlorhydria is said to be common but whether the incidence in these patients is greater than in normal persons of this age group has not been established

Treatment and Prognosis —The prognosis and treatment in cases of Felty s syndrome in so far as the joint manifestations are concerned is no different than in the usual case of rheumatoid arthritis It consists of appropriate rest physiotherapy methods the use of salicylates to relieve pain and an adequate balanced diet It should be remembered that rheumatoid arthritis is a chronic progressive disease for which there is no specific treatment although as discussed later gold therapy has been helpful in some patients

As a majority of the patients have a hyperplastic bone marrow demonstrable on sternal aspiration the criteria of hypersplenism are met namely cytopenia splenomegaly and hyperplastic bone marrow and the question

of *splenectomy* arises In the opinion of Dameshek (205) the splenomegaly may be present for some years prior to the development of the cytopenias When they do appear, however they may persist indefinitely unless splenectomy is performed

Two patients with this syndrome have been operated upon at the University Hospital In one a 55 year old male, following splenectomy the white blood cell count increased from a marked leukopenia to 14 850 per cubic millimeter with a good sustained neutrophil response Also there was a gain in body weight of 25 pounds in three months The second patient a female, aged 38 years had a white blood cell count of 2850 per cubic millimeter which increased to 8550 per cubic millimeter following splenectomy with a moderate deficiency of neutrophils There was improvement from a purely clinical standpoint From our limited experience it may be said that the benefit derived from splenectomy in this condition is not striking but in general it seems to be worth while in selected cases with evidences of hypersplenism Comments by other observers concerning the advisability of splenectomy are conservative although often there is a beneficial effect on the blood (206 207)

A comprehensive review of the literature dealing with Felty s syndrome has been contributed by Hutt Richardson and Staffurth (208) They consider that the syndrome is a variant of rheumatoid arthritis The neutropenia in their opinion is secondary to hypersplenism and they state that splenectomy will restore the leukocyte count to normal It is recommended by these observers that this operation be carried out in all cases provided there are no other associated disease states which would contraindicate it Following splenectomy in their own four cases of Felty s syndrome the patients showed a striking improvement in general health and the blood returned to normal in the period of one year in which the patients had been followed

Two of our patients with Felty s syndrome were treated with 100 milligrams of ACTH for six to 10 days respectively Several days after the appearance of the eosinopenia there was a neutrophilia associated with an increased granulocytic reaction in the bone marrow The leukocyte rises in the circulating blood however disappeared in seven and 11 days after the medication was omitted Although the blood changes were favorable they were not maintained following the discontinuance of the medication It must be concluded therefore for the present that such therapy exerts only a brief beneficial effect which is not sustained after treatment is stopped The results as far as the blood is concerned are encouraging and as the arthritic symptoms are also benefited it seems desirable to study additional cases with a longer period of treatment before coming to a final conclusion regarding this form of therapy

A case of Felty s syndrome treated with 100 milligrams of ACTH daily for 38 days has been reported by Bichel and Kissmeyer Nielsen (209) During the treatment the splenomegaly and the granulocytopenia dis

appeared The thrombocytes increased to almost normal values The arthritis and general condition of the patient improved With the withdrawal of ACTH the splenomegaly and abnormalities of the blood were reappearing when the report was written

Gold therapy should always be considered In one of my patients who received such treatment despite the presence of a pronounced leukopenia the immediate results were striking prompt and gratifying and the leukopenia was not increased In fact the white blood cell count was observed to rise during the administration of this therapeutic agent On account of the characteristic clinical picture and course of the disease in this patient the case history is given in considerable detail I W University Hospital number 475814 female age 45 years when I first saw the patient in 1941 She was referred because of a persistent leukopenia which had been observed for about one year in association with the characteristic findings of rheumatoid arthritis The patient had been recognized as having a psychoneurosis of the anxiety type for some years In 1939 two years before she came under my observation while on a trip to California she developed an attack of acute tonsillitis which was followed shortly by multiple migratory joint pains These cleared within a few weeks without residual joint deformity Six months later after a similar attack of joint pains structural changes characteristic of rheumatoid arthritis appeared in many joints

About five months later in April 1940 she was observed by a physician in the South who found evidence of rheumatoid arthritis and a red blood cell count of 3 6 millions per cubic millimeter with a hemoglobin of 60 per cent (9 4 grams) and a white blood cell count of 3500 per cubic millimeter The differential count was reported as normal" She continued to have a leukopenia with a count as low as 2400 per cubic millimeter at the time an eosinophilia as high as 12 per cent was observed On one occasion she had been given pentnucleotide which apparently had no effect on the low leukocyte count When first seen by me at the University Hospital in August 1941 she presented the typical deformities of far advanced rheumatoid arthritis with a red blood cell count of 4 0 millions per cubic millimeter a hemoglobin of 71 per cent (11 1 grams) a white blood cell count of 1450 per cubic millimeter with the following differential formula neutrophils 44 per cent large lymphocytes 17 per cent small lymphocytes 33 per cent monocytes 3 per cent eosinophils 3 per cent basophils 0 The platelets were normal in number as noted on the blood film The mean corpuscular volume was 88 cubic microns the mean corpuscular hemoglobin concentration was 31 per cent the saturation index 0 93 and the color index 0 88 The liver edge descended 8 to 10 centimeters below the left costal margin

Gastric analysis following the injection of histamine showed a low free acidity In the three years this patient s white blood cell count had fluctuated between 650 and 3300 per cubic millimeter With the count

of 650 the neutrophils were 62 per cent Following a course of gold therapy there was striking improvement in the joint manifestations a gain in body weight and sense of well being There was no deleterious effect on the already existing leukopenia The red blood cell count in August 1943 was 4 8 millions per cubic millimeter the hemoglobin was 84 per cent (13 grams) the mean corpuscular volume 82 cubic microns the mean corpuscular hemoglobin concentration 33 per cent saturation index 1 0 The improvement following gold therapy has been gratifying At no time was there evidence that the gold increased the leukopenia although several physicians who had previously examined the patient had feared that this might occur and hence had considered this form of therapy to be contraindicated

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CHAPTER XVI

THE LEUKEMIAS

Synonyms.—Leukocythemia, leukanemia, leukosis, leukosarcosis.

Definition.—Leukemia may be defined as a fatal disease, generally considered to be neoplastic in nature. It arises primarily in the blood forming organs and is characterized by a partial or complete absence of those factors which regulate the orderly growth and differentiation of the leukocytes and closely allied cells. This unrestricted proliferation of immature cells is responsible for the leukemic infiltrations which are to be found in the tissues throughout the body, especially the bone marrow, spleen and lymph nodes. Almost invariably at some time during the course of the disease immature white blood corpuscles appear in the circulating blood, frequently in great numbers. In most cases there is an associated myelophthisic anemia, often of a severe degree.

As Gall (1) says, leukemia may be defined as a lethal disease of the blood forming organs characterized by marrow and visceral infiltration and by tumor like overgrowths of one or another cellular component of the hematopoietic system. He points out that there are usually, but not necessarily, abnormal leukocytes in varying numbers in the peripheral blood. This definition very properly indicates a primary disease of the hematopoietic system involving the bone marrow, and the state of the circulating blood is regarded as having a wholly dependent and subordinate status. It is the opinion of Gall that the diagnosis of leukemia should be made only in those cases in which bone marrow studies have been completed, and this regardless of the changes which may be encountered in the peripheral blood.

History.—It is well established that the disease was first observed by Barth in 1839 and that the original microscopic examination was done by Alfred Donné. The circumstances are described by Dreyfus (2). The patient was first observed under the care of Barth on the service of Chomel at the Hotel Dieu. She was 44 years old and was found to have a tumor, undoubtedly the enlarged spleen, extending from the left hypochondrium to the inguinal fossa, with the medial border reaching the midline. After death the blood was examined by Donne, who reported that more than one half of the cells were "mucous globules" and commented that "that as you know, the pus cell cannot be differentiated with definite accuracy from mucous cells." Furthermore Donné observed another case during life which he reported in his treatise on

Microscopy published in 1844 (3) This patient was a male seen at the Hospital de la Charite who had ecchymoses and gangrenous blisters involving the skin of both legs He says the blood showed such a number of white cells that I thought that his blood was really mixed with pus Although it is accepted that this is the earliest microscopic examination of the blood in the disease the observation was not published until the year 1844 (3) and the description by Barth did not appear until the year 1855 (4) Very properly a question arises concerning the priority because although the observations were made in 1839 their publication did not occur until the years 1844 and 1855 respectively Even then however it should be emphasized Donne s publication dealing with the microscopic examination of the blood appeared in the year 1844 preceding the reports of Craigie (5) of Bennett (6) and of Virchow (7) by one year

Of great interest is the fact that a then 25 year old Scottish physician John Hughes Bennett attended lectures given by Donne in Paris and hence probably became familiar with his knowledge of the changes in the blood of such persons

By many it has been considered that the earliest accurate descriptions of leukemia with a microscopic examination of the patient s blood were published almost simultaneously and independently in the autumn of 1845 by John Hughes Bennett of Edinburgh and Rudolph Virchow of Berlin Details of the case were published by Bennett in the *Edinburgh Medical and Surgical Journal* on October 1 1845 (6) whereas the case of Virchow appeared six weeks later in November 1845 (7) In the Edinburgh publication there were two cases presented the first by Craigie and the second by Bennett

It seems clear to me that Craigie is less deserving of credit for his presentation than the other two observers This is because his patient had been observed in 1841 four years previously and the pathologist s report was to the effect that the blood "contained globules of purulent matter Craigie explained that he published the case in 1845 because the occurrence of the case in many if not in all respects similar to that of another physician in the same hospital led me to anticipate similar results and went far to confirm my conclusions deduced from the first case Apparently Bennett did not agree with Craigie s statement for according to Rolleston (8) after Craigie s death it was stated by Bennett that the significance of the blood changes was not appreciated by Craigie or even remembered until they were found in the second case

Bennett reported his case under the title Case of Hypertrophy of the Spleen and Liver in which Death Took Place from Suppuration of the Blood A necropsy was performed by Bennett and the blood examined under the microscope He described the blood as resembling thick creamy pus and stated that microscopically they presented all of the

appearances of pus corpuscles. He regarded the condition as attributable to a pyemia.

A few weeks later the report of Rudolph Virchow appeared in the November number of *Froneps Notizen* for 1845 (*7*). In this publication a patient was described in whom the proportion between the white and red corpuscles was reversed and the condition was attributed to an increase in the number of white corpuscles. Virchow refers to the older descriptions of white blood as "quite useless because the microscopic examination is missing but he was apparently not familiar with the published report concerning the microscopic appearance of the blood by Donné which had appeared the year before (*3*). He refers to another case reported by Lautner (*9*).

To Virchow undoubtedly the credit must go for the view that the colorless cells of the circulating blood, which were present in such great numbers, were not pus and as Osler (*10*) says "Virchow vindicated a place in pathology for the white blood corpuscle." In the January 1847 number of *Medicinische Zietung des Vereins fur Heilkunde in Preussen* Virchow (*11*) reviews a number of cases of white blood which he had collected from the medical literature. These were the cases of Bichat (1801) Velpeau (1827), Caventon (1828), Andral (1839) Barth (1839).

It is easy to understand why the circumstances concerning priority gave rise to a historical controversy which at the time grew somewhat acrimonious. The fairest conclusion concerning the merits of the claims was given in 1885 by William Osler (*10*). He says Bennett certainly described cases before Virchow but only in a manner in which Bichat Velpeau and others had previously done and Bennett distinctly stated his belief that the gray white matter was composed of pus. Virchow from the first grasped the idea that the altered state of the blood was due to an increase in the colorless cells and he first suggested the relation between their increase and the condition of the spleen and lymph glands and he first gave a satisfactory name to the disease so that while acknowledging the great and valuable services of Bennett we must perforce recognize the greater merit of Virchow and recognize his priority in the scientific description of the disease and in giving it a suitable name. The further investigations of Virchow enabled a splenic and lymphatic form to be recognized ..." On the other hand Gowers (*12*) has this to say in regard to the controversy. Opinion on this point will depend on the view held as to what constitutes a discovery. It is certain that the disease was first fully observed by Donné and Barth and first fully described by Craigie and Bennett.

The word leukemia was originally employed by Virchow in 1847 but Bennett objected to the use of this term on the ground that the blood was not white and contended that the term leucocythemia as he first spelled

it in English meaning white cell blood more correctly described the condition A discussion concerning the use of the term leukemia is given by Gowers in 1879 (*12*) He says the name (leucocythaemia) proposed by Bennett is preferred to that of Virchow (leukaemia) on the ground that as pointed out by Parks the blood is never white and rarely approximately so that the term white blood had before been applied to a totally different condition and that the term of Bennett describes what is universally taken as the diagnostic sign the microscopical condition of the blood

In 1846 H W Fuller (*13*) gave a description of the blood of a patient with leukemia during life as well as the necropsy findings Vogel in 1849 (*14*) was the first to make a similar observation in Germany Virchow in 1847 described the two forms lymphatic and splenic and Neuman in 1870 recognized a third type the myelogenous In 1852 Hughes Bennett (*15*) published a monograph on the disease which contained a number of new cases

The term pseudoleukemia was introduced by Cohnheim in 1865 (*16*) to describe a condition in which the lymphatic glands showed the histologic picture which with the knowledge of the day suggested leukemia As there were no significant blood changes it is likely that the condition was either subleukemic leukemia or Hodgkins disease

Leukemia was first recognized in childhood by Biermer in 1861 (*17*) and by F V Birch Hirshfield in 1878 (*18*) Friedrick (*19*) reported an acute case of leukemia in 1857 and 1895 A Fraenkel (*20*) gave a description of the immature white blood cells in this condition

The increase in the basal metabolic rate was first described in 1911 by Grafe (*21*)

Ehrlichs discovery in 1879 (*22*) of specific staining methods provided a hitherto unavailable accurate means of recognizing the various types of white blood cells By the application of this technic it was found that the splenic type of leukemia as described by Virchow and the medullary type of Neuman were identical and hence the term spleno myelogenous leukemia *had been used for what we now call myelogenous leukemia* This resulted in a pseudo simplification of leukemia into two great groups the myelogenous in which there were granulocytes in excess in the circulating blood and the lymphatic in which the lymphocytes predominated

There remained however a large group which could not be assigned to either one of these large groups The discovery by Otto Naegeli in 1900 (*23*) of the myeloblast and accurate means of its identification led to the finding that many of these atypical leukemia cases were in truth different phases of myelogenous leukemia Confirmation of the studies of Naegeli was accomplished by the aid of the oxidase and peroxidase stains by Graham and others (*24*) Even with the recognition of the

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The word leukemia was originally employed by Virchow in 1847 but Bennett objected to the use of this term on the ground that the blood was not white and contended that the term leucocythemia" as he first spelled

it in English meaning white cell blood more correctly described the condition A discussion concerning the use of the term leukemia is given by Gowers in 1879 (*12*) He says "the name (leucocythaemia) proposed by Bennett is preferred to that of Virchow (leukaemia) on the ground that, as pointed out by Parks the blood is never white and rarely approximately so that the term white blood had before been applied to a totally different condition and that the term of Bennett describes what is universally taken as the diagnostic sign the microscopical condition of the blood

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The term pseudoleukemia was introduced by Cohnheim in 1865 (*16*) to describe a condition in which the lymphatic glands showed the histologic picture which with the knowledge of the day suggested leukemia As there were no significant blood changes it is likely that the condition was either subleukemic leukemia or Hodgkin s disease

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There remained however a large group which could not be assigned to either one of these large groups The discovery by Otto Naegeli in 1900 (23) of the myeloblast and accurate means of its identification led to the finding that many of these atypical leukemia cases were in truth different phases of myelogenous leukemia Confirmation of the studies of Naegeli was accomplished by the aid of the oxidase and peroxidase stains by Graham and others (24) Even with the recognition of the

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Introduction of the Roentgen Ray in the Treatment of Leukemia and Pseudoleukemia—Apparently the first cases of pseudoleukemia treated with the x rays were demonstrated by William Allen Pusey of Chicago before the Chicago Medical Society on February 26 1902 Also at that time reference was made to a case of splenic leukemia which had been treated with the x rays In regard to the latter case Pusey (26) says that he treated a woman age 50 with an enormous spleen 3 0 million red blood cells and 300 000 white blood cells per cubic millimeter Accord ing to him *she was given x ray exposures for over a month with no effect* whatever The exposures were not however carried to the point of producing any apparent effect on the skin and in my judgment the case showed nothing Apparently this is the first reference to the use of the roentgen rays in the treatment of leukemia and is of historic interest despite the fact that the treatment was unsuccessful Pusey also says that in his book, *Roentgen Rays* published in June 1903 he records a case of leukemia which he had treated successfully with the x rays between November 1901 and February 1902 with a disappearance of almost all of the tumors Information relating to the early contribu tions concerning the effect of the roentgen ray on pseudoleukemia and leukemia is given in a letter written by Pusey to the *Journal of the Ameri can Medical Association* in 1904 (27) The main purpose of this letter was to correct the inference by Senn that he had been the first to treat pseudoleukemia and leukemia by means of the roentgen ray Nicholas Senn had written a paper which appeared in the *New York Medical Journal* for April 18 1903 in which he reported that two cases of pseudoleukemia had been successfully treated by means of the x ray Also in the *Medical Record* for August 22 1903 Senn (28) had reported A Case of Spleno myelogenous Leukemia Successfully Treated by the Use of the Roentgen Ray No reference was made to the prior work of Pusey and others

Interesting information bearing on the early history of the treatment of leukemia with the roentgen ray was given to me by the late Dr Cecil M Jack of Decatur Illinois He says In the spring of 1903 I attended a clinic of Dr Nicholas Senn at the Presbyterian Hospital Chicago and he showed a case of myelogenous leukemia which was being treated with x ray I was then assistant to Dr E J Brown in Decatur When I returned home I told Dr Brown of this wonderful result of Senns so he gave me a case to try out I treated the case and got the facts together and Dr Brown published a preliminary note concerning it (29) Dr Senn reported the case I saw in Chicago in August 1903 (30)

The patient first treated with x ray by Dr Jack died and a postmortem was performed by him and sections examined The ultimate failure of the roentgen rays in the treatment was reported with reference to this case by Drs Brown and Jack (31) Dr Jack states This is probably the first case so treated in which complete postmortem findings were given Dr Carl Weller, now Professor of Pathology at the University of Michigan Medical School tells me he is still using the kidney slides of this case in his teaching of medical students to show calcification Dr Jack gives some interesting information concerning the method of treatment which he employed in the management of his patient He says In my case I continued treatment until the white blood cell count was as low as 7000 per cubic millimeter The spray method was used although I did not know it Three feet was the distance and as I remember the patient reclined on a low couch and the tube was placed as high as the tube stand would allow We knew nothing about R units but were careful to not produce a dermatitis No screening was used either for the patient or the operator We used a Wagner Micaplate machine One hundred and six treatments were given The patient died of an aleukemic leukemia

Another early article dealing with the roentgen ray treatment of a patient with myelogenous leukemia was written by Lawrence C Grosh and Willard Stone (32) It was entitled Roentgen Ray Treatment of Leukemia The patient improved with x ray therapy but died unexpectedly Their necropsy findings were reported The earliest use of the x ray in the treatment of leukemia in 1902 was seven years after the epoch making discovery of William Conrad Roentgen who announced it to the world with the title On a New Kind of X Ray" (33)

Development of Knowledge of Leukemia in Animals—Leukemia in the horse was first recognized by Leisering in 1858 (*34*) in 1865 the same author noted the condition in swine (*35*) It was first described in the mouse in 1874 by Eberth (*36*) In 1868 it was recognized in fowls by Roloff (*37*)

Although unsuccessful attempts were made by Mosler in 1872 to transmit leukemia from one animal to another (*38*) it was not until Ellermann and Bang in 1908 transmitted erythroleukemia and myelogenous leukemia from diseased to healthy birds that the first successful transmission experiments were performed (*39*)

That a hereditary influence might be of importance in the etiology of leukemia was first expressed by Hartenstein in 1896 who observed lymphatic leukemia in a cow and its mother (*40*) In 1931 Slye concluded from her studies in mice that leukemia like other neoplastic diseases is transmitted as a simple Mendelian recessive characteristic (*41*) The first definite information determining the inheritance of leukemia in mice became available when MacDowell and Richter published their

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It is not possible to explain this increased incidence on the basis of the recognized fact that more persons survive to old age for the death rates from the disease have increased in all of the age groups (*48*) Undoubtedly the disorder is recognized more frequently as the result of improved diagnostic facilities especially the more widespread use of sternal puncture with which the diagnosis of the aleukemic and sub leukemic types is made more readily In my opinion however this accounts for only approximately one half of the increased incidence

Leukemia can no longer be regarded as a rare disease It has been stated that (*48*) in 1942 this disease accounted for more deaths than those due either to smallpox meningococcus meningitis scarlet fever poliomyelitis malaria typhoid fever and diphtheria combined The death rate from leukemia is now higher than that of the anemias whooping cough the dysenteries or alcoholism It is estimated that more than 5000 deaths occur annually in the United States from this disease

Classification —The leukemias may be classified on the basis of (1) the acuteness of the disorder (2) the presence of the leukemic or subleukemic (aleukemic) phase in the blood and (3) the parent cell type Anyone who has investigated the subject will agree that there is considerable confusion in regard to the classification of the various parent cell types of the disease particularly of the acute leukemias To a lesser extent there is disagreement on the existence nature and frequency of monocytic leukemia In recent years it has been determined that lymphosarcoma leukemia can be separated from lymphogenous leukemia Aside from these three points there is usually very little difficulty in recognizing the variety of leukemia which is present in any given patient

The differentiation of acute from the chronic leukemia is usually easily accomplished The differential points are 1 the duration of the disease 2 the severity of the process and 3 changes in the peripheral blood In acute leukemia the expected duration of life is less than three months from the onset of the symptoms in subacute leukemia it is three months to one year and in chronic leukemia it is from one to 20 years or longer These criteria cannot be applied too rigidly however as a patient with a leukemia of some years duration may develop an acute exacerbation with all of the classical clinical manifestations of an acute process True acute leukemia has a relatively brief course usually without remissions terminating fatally in an interval usually averaging between several weeks to several months

The severity of the process must also be taken into account when differentiating between the acute and chronic types of the disease In acute

paper in 1935 (*42*) Following the 18 generations of brother sister matings, 90 per cent of the offspring in this strain had leukemia, chiefly of the myelogenous type Evidence that irradiation could increase the incidence of leukemia in mice was first presented by Krebs Rask Nielson and Wagner in 1930 (*43*)

Incidence —The incidence of leukemia is difficult to estimate with accuracy for several reasons In the first place the condition has not always been recognized in the past because the blood was not examined, and to a certain extent this criticism is still true A superficial blood examination even by a novice suffices to make the diagnosis in a patient in whom the leukocyte count is greatly elevated and a fairly large number of immature white blood cells are present in the circulating blood In the case of patients with the subleukemic variety of the disease however, the diagnosis is frequently missed This is because the white blood cell count is normal or a leukopenia is present and only small numbers of immature cells are in the circulating blood In such patients it is frequently the associated severe anemia which attracts the most attention and not uncommonly the real nature of the disease process is overlooked hence the condition is regarded as anemia of unknown causation or attributed erroneously to some other cause than leukemia With a more widespread knowledge concerning the characteristic changes in the blood in subleukemic leukemia and the employment of sternal puncture which is exceedingly useful in the diagnosis of the subleukemic forms of the disease, an increasing number of these cases will be recognized

Necropsy statistics however furnish fairly reliable evidence of the frequency of the disorder and indicate that it occurs in something less than 1 per cent of all cases examined in a general hospital For example, Ikeda (*44*) found 77 cases of leukemia in the records of 12 396 necropsies at the University of Minnesota which gives an incidence of 0 62 per cent or one in 161 postmortem examinations Kirshbaum and Preuss (*45*) reported that 123 cases of leukemia were observed in 14 400 consecutive autopsies performed at the Cook County Hospital between the years 1929 and 1941 which is a rate of one in 117 or 0 86 per cent An incidence of 0 79 per cent or one in 126 was reported in a group of 26 394 necropsies by Krumbhaar and Stengel (*46*) It has been estimated by Nielsen that one case of leukemia occurs per 50 000 population in Denmark Wintrobe (*47*) quoting from the statistics of the Metropolitan Life Insurance Company states that there were 3500 deaths due to leukemia in the United States annually between 1934 and 1936 which is approximately as many as were caused by diphtheria measles or typhoid fever and almost as many as resulted from malaria

There is some indication that there is a real increase in the incidence of leukemia This is suggested by the fact that in the 15 years in which our group of 495 cases were observed at the Simpson Memorial Institute

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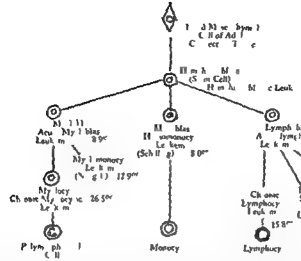

FIG 60—The above diagram shows the development of the different types of white blood cells and indicates how such cells serve as a basis for the development of the different varieties of leukemia The number in percent adjacent to the various cell types indicates the percentage of such cases of leukemia we have observed at the Simpson Memorial Institute in a group of 495 patients with the disease All cases are classified according to three parent cell types the lymphoblast the myeloblast and the monoblasts These cells are considered as arising from the undifferentiated or but slightly differentiated reticulum cell (histioblast or histiocyte) In some instances such extremely primitive cells may make up the predominating cell type in leukemia The three main divisions are designated respectively as the myelogenous the lymphogenous and the monocytic The myelogenous leukemia group is subdivided into the myeloblastic the myelocytic and the myelo-monocytic groups The Lymphogenous group is divided into the lymphoblastic the chronic lymphatic and the lymphosarcoma group Also included in the lymphocytic group for convenience but with questionable correctness is the plasma cell type Monocytic leukemia derived from the monoblast is of the Shilling type

leukemia the patient is usually critically ill and profoundly prostrated In most cases there is also a high fever and a hemorrhagic tendency On the other hand in chronic leukemia the course of the disease may be comparatively mild at least for long periods of time

The blood changes in the acute and chronic forms are usually very striking In general the differential points are (1) the intensity of the anemia and (2) the percentage of immature white blood cells As these changes are discussed in detail under the section dealing with the various types of leukemia only brief mention will be made of them here In acute leukemia there is usually a rapidly developing and severe anemia and 50 per cent or more of the white blood cells present in the circulating blood are of the immature type In chronic leukemia the red blood cells and hemoglobin may be normal or if an anemia is present it develops at a much slower rate and is usually not as severe as in the acute forms except in the terminal stage Furthermore the number of immature white blood cells in the peripheral blood in chronic leukemia is below 50 per cent and in many instances these cells may not comprise more than

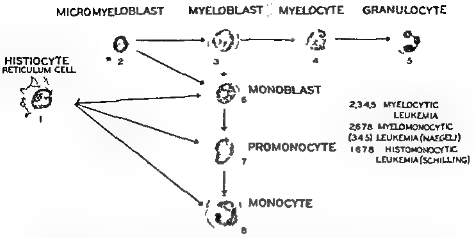

Fig 61 —The above figure illustrates the view expressed by Downey relating to the types of monocyte leukemia The histocyte gives rise to the micromyeloblast which in turn develops into the myeloblast the myelocyte series and the mature granulocytes Leukemia involving this group is either myeloblastic or myelocytic The micromyeloblast also according to Naegeli may be transformed into the monoblast and it is such cells which are present in the Naegeli type of myelomonocytic leukemia The peripheral blood in such patients contains a predominance of monocytes in various stages of maturity along with monoblasts and young myelocytes This condition is designated as monomyelocytic leukemia (Naegeli) In histomonocytic leukemia the histiocyte is thought of as giving rise to the monoblast then the promonocyte and finally the monocyte It is a disturbance of this normal arrangement which is seen in histomonocytic leukemia (Schilling) (Bethell courtesy *Annals of Internal Medicine*)

10 or 15 per cent of the total number It should be kept in mind however that at any time the chronic type of leukemia may change and the characteristic alterations of acute leukemia appear in the blood

The differentiation of the aleukemic and subleukemic forms of leukemia is based solely on the number of white blood cells in the circulating blood A useful arbitrary classification is as follows leukemic leukemia the leukocyte count is above 15 000 per cubic millimeter with the type cells predominating subleukemic leukemia the leukocyte count is below 15 000 per cubic millimeter yet with the type cells present in sufficient numbers to indicate the diagnosis aleukemic leukemia the leukocyte count is below 15 000 per cubic millimeter yet the type cells are absent from the blood or so few in number that the diagnosis cannot be made by examination of the blood alone

Classification of the leukemias may be made on the basis of the parent cell type namely the lymphoblast the myeloblast or the monoblast Reference to Figure 60 will show that occasionally there is a type of acute leukemia in which the cells are almost entirely of the most primitive type called hemohistioblasts A leukemia of this nature is designated as hemohistioblastic leukemia These terms are synonymous with stem cells and stem cell leukemia

TABLE XXXII

	Per Cent
Chronic Myelocytic Leukemia	26.5
Lymphosarcoma Cell Leukemia	16.2
Chronic Lymphogenous Leukemia	15.[illegible]
Acute Lymphoblastic Leukemia	11.7
Acute Myeloblastic	8.9
Myelo-monocytic (acute)	8.5
Histo monocytic (acute)	4.8
Myelo monocytic (chronic)	4.4
Histo monocytic (chronic)	3.2

The main divisions of leukemia are the lymphogenous, myelogenous and monocytic leukemia. The subdivisions of the lymphogenous are the acute (lymphoblastic), chronic (lymphocytic), and the lymphosarcoma cell (acute or chronic). The myelogenous type is divided into the acute (myeloblastic), the chronic (myelocytic), and the myelo monocytic. The latter subdivision is based upon the theory of Naegeli that possibly there is a transition from the myelocyte to the monoblast with the subsequent formation of the mature forms of monocytes in the blood stream. It would be considered, therefore, as one of two forms of monocytic leukemia. Monocytic leukemia of the histio monocytic type of Schilling is characterized by a proliferation of the cells of the reticulo endothelial system which develop into monocytes of the blood. By some this is the only form of monocytic leukemia which is recognized—the Naegeli type, as stated above, being considered as a myelogenous leukemia with a monocytic reaction. In the myelogenous group are included the rarer forms of leukemia, such as chloroma, eosinophilic, basophilic and megakaryocytic leukemia. Plasma cell leukemia is possibly related to lymphogenous leukemia.

Incidence of Various Types of Leukemia.—In the 15 years from 1927 to 1941, 495 cases of leukemia were observed at the Simpson Memorial Institute of the University of Michigan. According to Bethell (49), 43.6 per cent were of the lymphogenous type, 48.3 of the myelogenous and 8.1 per cent monocytic (histogenous or Schilling type). If the myelo monocytic variety were removed from the classification of myelogenous leukemia, the percentage of cases in this subgroup would be 35.4 per cent and if they were added to the monocytic variety, it would increase this division to 21 per cent. The order of frequency of the various types of the disease in the 495 cases is shown in Table XXXII.

It is of interest to note that one third (33.6 per cent) of the acute leukemias were of the subleukemic type. Furthermore, almost one half of the chronic varieties were similarly classified as subleukemic. In the acute lymphogenous and the lymphosarcoma cell leukemias the subleukemic varieties predominated.

The incidence of the various types of leukemia as reported in a group of 123 cases by Kirshbaum and Preuss (45) is as follows lymphogenous leukemia 30 8 per cent myelogenous leukemia 43 1 per cent monocytic leukemia (Schilling type) 4 1 per cent stem cell leukemia 22 7 per cent These figures are in fairly good agreement with the exception that in the group studied by Kirshbaum and Preuss a relatively large per cent of the cases (22 7 per cent) were classified as the stem cell type whereas Bethell completely omits this variety in his classification

This difference illustrates the difficulty in attempting to group logically the various types of acute leukemia Apparently Bethell considers that it was possible to differentiate the various types of cells in the acute phase of the disease into myeloblasts lymphoblasts and monoblasts whereas Kirshbaum and Preuss believe that these cells are of the undifferentiated or stem cell type (hemohistioblasts) The entire problem of classification of the acute leukemias in final analysis is based on one's ideas concerning the identification of the various types of primitive white blood cells or their precursors Hence with the present state of our knowledge there is likely to be an honest difference of opinion concerning this matter until universally acceptable criteria of the various types of primitive white blood cells are recognized

Age and Sex—The various types of leukemia may occur at any age but there are certain predilections of the disease for the different decades of life There is also a difference in the incidence of the condition in the two sexes which is definitely recognized but for which there is no explanation at present

Acute lymphoblastic leukemia occurs most commonly in children and as Bethell says is a cataclysmic disaster of childhood The majority of all cases of acute leukemia are observed in the first decade of life beginning and terminating in 90 per cent of instances before the age of 20 years Its greatest incidence is in children under the age of five years Rarely does it occur after the age of 50 years but it may develop at any period of life and has been reported in old age After the second decade of life *myeloblastic leukemia replaces lymphoblastic leukemia as the most* common form of acute leukemia The highest incidence in our series of the acute monoblastic leukemia including both the Naegeli and Schilling types was between the ages of 30 and 60 years

It has been emphasized by Cooke (50) that the acute forms of leukemia are far more common in children than adults and that younger children are more frequently affected than older ones According to this observer in the third decade acute leukemia occurs far less frequently than in the second and after the age of 30 years it is relatively rare as compared with the earlier ages It is also stated that in the acute forms of the disease as well as the chronic types seen in adults males are more commonly affected than females the figures showing from 60 to 79 per cent of males in the

various groups reported. After a study of 1500 cases of acute leukemia in children admitted to 33 children's hospitals of pediatric services in the United States and Canada during a period of years the following conclusions are deduced by Cooke. (1) During childhood there is a gradual increase in the proportion of males over females who have acute leukemia the predominance of boys being greater in later childhood than in infancy. In the first year of life more cases are observed in girls than boys. (2) The age incidence follows a regular curve which rises from a moderate elevation in the first two years of life to a peak of highest incidence in the third and fourth years with a sharp decline in the next three years, and a more gradual progressive fall throughout the latter half of childhood."

Lymphocytic leukemia is the predominating form of chronic leukemia after 60 years of age and is rarely observed before the age of 40 years. Among our group of patients there was only one patient in the latter group, a woman age 28 with the disease. Women have a tendency to be affected with the disease at an earlier age than men, as shown by the fact that 60 per cent of the males were more than 60 years of age whereas 80 per cent of the women were less than 60. Sixty two per cent of the entire group of patients with chronic lymphatic leukemia were males which is somewhat less than the incidence reported by other observers. The case of a male age 84 years, with chronic lymphatic leukemia is reported by Tidswell (51) who reviews the subject of leukemia in elderly patients.

Lymphosarcoma cell leukemia is observed at all ages, for it is recognized that lymph tissue may undergo sarcomatous change at any period of life and subsequently the neoplastic cells may break through the restraining connective tissue capsule and reach the circulating blood. Fully developed lymphosarcoma cell leukemia may occur at any age in females. In males, however the incidence of the disease roughly parallels that of acute lymphoblastic leukemia in childhood and chronic lymphocytic leukemia in adult life. Between the years of 10 and 40 both sexes are affected equally with the disease but outside of these limits there is a predominance of males with the disease. Of the entire series of our patients with lymphosarcoma cell leukemia 70 per cent were males.

Myelocytic leukemia is the most frequently encountered form of the chronic type of the disease up to the age of 60 years after which the lymphocytic is most frequently observed. In our group of patients chronic monocytic leukemia of both the myelo monocytic (Naegeli) and the histio monocytic (Schilling) types was most frequently encountered between the ages of 30 to 60 years without showing predilection for any single decade.

In summary therefore it may be said that acute leukemia is most commonly found in childhood and young adult life myelogenous leukemia is the predominating variety of the chronic disease until the age of 60 years after which chronic lymphatic leukemia is more frequently

encountered. It is exceedingly rare in the females to observe chronic lymphatic leukemia before the age of 40 years. Lymphosarcoma cell leukemia has no definite predilection for age in females, but in males it occurs more commonly before the age of 20 years and after the age of 60. Chronic monocytic leukemia is most commonly found between the ages of 30 and 60, but no special decade was found to have an especially large group of cases. The acute variety of monocytic leukemia occurred most commonly between the ages of 30 to 40 years. In general, it may be said that leukemia is more commonly observed in the male than the female sex, but there are some exceptions to this statement which are noted above.

Etiology.—The Nature of Leukemia.—The cause of leukemia is unknown, but the prevailing view considers the condition to be neoplastic in nature. It is conceded by all that the disorder is an invariably fatal, invasive pathologic process. Much important basic information concerning the nature of the disorder has been derived from a study of the disease in three species of mammals, namely, the guinea pig, the mouse and the rat. Studies in all of these have yielded essentially the same results. It has been demonstrated that the disease is readily transmissible from one animal to another provided there are living leukemic cells in the inoculum. These cells multiply in the inoculated animals without restraint and reproduce themselves without completing the normal maturation cycle. In the words of Furth (52) "the leukemic cells are malignant," and hence can be designated as malignant myelocytes, lymphocytes, or monocytes. Furth (52) further states that the leukemic cells in animals have certain individual characteristics which include: (1) morphological peculiarities, (2) the ability to invade the blood stream or, on the other hand, to keep out of the circulation irrespective of the route of inoculation, (3) the ability to produce tumors or diffuse infiltrations, (4) a tendency to localization in different organs, and (5) the production of a secondary anemia or of a hemorrhagic diathesis.

Observations concerned with transmissible and spontaneous leukemia in mammals indicate that there is a different mechanism of inheritance. Susceptibility to transmissible leukemia is a dominant characteristic, but this is not true of the spontaneous disease. From breeding experiments in animals it is known that the incidence of spontaneous leukemia is lower in the first generation of hybrids than in the parental stock. Slye (53) explains this by assuming a single recessive gene as responsible for the occurrence of leukemia and an additional localization factor. In animals it is considered by Furth that the leukemic cells are *potentially neoplastic* and are inherited as a unit in a group of cells. They are not, therefore, merely supernumerary cells misplaced in a haphazard manner but are inherited according to genetic laws. The neoplastic transformation of these cells indicates that they are born as normal but are destined at a given age to undergo a pathological change. This malignant meta

morphosis may be assumed to be analogous in some respects to a regressive cellular change process which does not result in cell degeneration. Instead there is an alteration in growth capacity often accompanied by cytological and other biological changes. The pathogenesis of transmitted leukemia in animals therefore may be explained adequately by assuming the introduction of malignant cells which grow without restraint in a susceptible host.

Relation of Animal to Human Leukemia.—It is interesting to note that a leukemia-like disturbance usually called leukosis has been observed to occur in several varieties of birds. Its transmission has been accomplished by means of a filtrable virus. Even though it is demonstrated that a filtrable virus will transmit the disease in animals, this is not incompatible with the view that leukemia is a neoplastic disease. Both experimental studies on animals and clinical observations on man make it extremely unlikely that there is a leukemic virus which spreads from animal to animal or man to man as an infective agent. It has been suggested (52) that leukemic cells may harbor an agent which is possibly enzyme-like in nature and that this accounts for the metamorphosis of normal to malignant cells. It should be emphasized, however, that the only reason for considering such a possibility is the existence of a leukemoid condition in birds.

There is a very close similarity between leukemia in man and the lower mammals. The presence in the tissues of myeloid cells, lymphocytes or monocytes in human cases resembles closely the leukemic infiltrations in animals having the various spontaneous or transmitted varieties of the disease. The acute and chronic forms of leukemia are found in both man and animals with high and low leukocyte counts and with diffuse infiltrations and tumor formations in addition to transition forms between lymphosarcoma and leukemia. There is conclusive proof that these types of leukemia are malignant in lower mammals, which suggests strongly that the same is true in man.

Spontaneous leukemia has not only been observed in lower vertebrates but in many kinds of birds. It has been recognized in domestic fowls, turkeys, geese, ducks, pigeons, swans, storks, parrots, canaries and vultures. The disorder has been studied in horses, monkeys, cats, dogs, sea lions, buffaloes, deer, goats, elephants, sheep, opossums, rats, mice and guinea pigs.

Spontaneous leukemia in animals occurs most frequently as the lymphogenous or lymphosarcoma form. But myelogenous leukemia has been observed; well developed cases of myelogenous leukemia and stem-cell leukemia have been observed in mice and rats and acute cases of monocytic leukemia in mice. Likewise lymphogenous leukemia, usually of the subleukemic type, may be present in fowls.

A most comprehensive discussion of spontaneous and experimental leukemia in animals is given by Engelbreth Holm (54).

In a study of eight inbred stocks of mice varying in susceptibility to the spontaneous disease it was found by Kirschbaum and Mixer (55) that multiple agents (hydrocarbon carcinogens x rays and estrogens) were capable of inducing leukemia in mice The effectiveness of each agent however depended on the genetic constitution of the stock involved In the opinion of these investigators leukemia may represent one type of neoplastic response to any one of several agents Their experience shows that x rays are the only agent which is almost universally leukemogenic for mice estrogens are probably second in effectiveness and carcinogenic hydrocarbons third

The Experimental Production of Leukemia—It is stated by Furth (52) that the following agents can be regarded as having produced leukemia in animals under controlled experimental conditions benzol indole methylchloranthrene and benzpyrene Methylchloranthrene and benzpyrene are among the most effective carcinogenic agents known It is thought that these substances when producing leukemia must come in direct contact in some unknown manner with the cells which they stimulate

The application to the skin of tar in mice can increase the incidence of spontaneous leukemia in animals For instance it was shown by Brues and Marble (56) that painting the skin with this substance in a strain of mice increased the frequency of lymphoblastosis and lymphatic leukemia from 2 to 50 per cent Furthermore with three samples of tar the frequency of the lesions increased with the carcinogenic activity

A most valuable and comprehensive survey of the facts in regard to experimental mammalian leukemia is made available in a recent article by Kirschbaum (57) The following statements concerning the present status of our knowledge concerning this phase of leukemia are based largely on the above summary of our knowledge

It is known that mouse leukemia occurs in a large proportion of mice of several inbred strains the disease may be induced in others by various means which will be discussed later It appears to be accepted that mouse leukemia is probably the same disease as that observed in man and all observers agree that the experimental evidence is in favor of the view that rodent leukemia is of a neoplastic nature There is a close relationship between lymphosarcoma and leukemia which leads to the conclusion that they are probably different morphological manifestations of the same fundamental disease process The evidence indicates that it is not possible to transmit mammalian leukemia by the inoculation of tissue extracts or blood plasma passed through bacterial filters nor is the disease transferable by the inoculation of fragments or ruptured cells Mammalian leukemia is transferable *only* by inoculation of living leukemic cells into a susceptible host usually of close genetic relationship Other factors which may modify transplantation are x ray partial immunization adrenal hormones and an increase in cellular malignancy It is

of interest to note and possibly of importance from the standpoint of future treatment, that immunity to transplanted leukemia may be accomplished by various means. Among these are the inoculation of sublethal doses of cells, injections of suspension of normal tissue cells of certain genetic constitution, the administration of heat killed leukemic cells, ultracentrifuged leukemic cell extracts or normal defibrinated blood. Furthermore, immunity has been conferred passively by the inoculation of liver and spleen of immune animals. According to Kirschbaum it has not been possible to immunize against either the spontaneous disease or the cells of a spontaneous case of leukemia.

It is possible to induce leukemia in susceptible mice by various agents. Among such agents are carcinogens, the roentgen rays, estrogens, and the unknown factors responsible for the production of the spontaneous disease. Mice of certain genetic constitution are susceptible to only certain agents. It is of interest to note that genetic susceptibility to one leukemogenic agent does not necessarily indicate that the animals are also susceptible to others of a different nature.

Uniform results have not been reported in studies on the genetics of mouse leukemia. Whether this discrepancy is apparent or real is a matter which depends on whether or not the data of various investigators are comparable. It is accepted that the breast milk of certain strains of mice contain a substance which influences the total incidence of leukemia in genetically susceptible animals. Also it is known that feeding a diet low in cystine will cause a reduced incidence of carcinogen induced leukemia; a decrease in the lysine of the diet has no such effect. Underfeeding will lower the incidence of death from spontaneous leukemia in a high leukemia strain of mice. Furthermore, recently Saxton, Boon and Furth (58) have shown that spontaneous leukemic transformation of cells can be delayed but not entirely prevented by underfeeding mice of the high leukemic Ak stock. The incidence was reduced from 65 to 10 per cent. A variation in the amount of fat in the diet has no influence on the onset of leukemia; a high fat diet, however, will prolong the induction time of methylcholanthrene induced leukemia.

Although the relation of leukemia to estrogens is of some importance to the induction of the condition in mice, it is much less so than in the relation to mammary cancer in the same animals. It is known that the incidence of leukemia in females is greater in certain strains, and large doses of estrogens have been shown to be leukemogenic for certain strains of mice. It has been reported that the absence of adrenal secretion favors the growth of rat leukemic cells. Heilman and Kendall (59) have shown that there is regression of a transplanted lymphosarcoma of the mouse when crystalline hormone of the adrenal cortex is administered. Recent experiments have suggested that the thymus gland might in some unknown manner influence the development of spontaneous leukemia in mice. Studies on the metabolism of mouse leukemia tissues indicate that

TABLE XXXIII

TYPE OF DISEASE AMONG FAMILIAL CASES

	No. of Cases
Lymphatic Leukemia	13
Myeloid Leukemia	2
Lymphatic and Myeloid Leukemia	6
Unknown Forms of Leukemia	5
Lymphatic and Unknown Forms of Leukemia	2
Myeloid and Unknown Forms of Leukemia	3
Total	31

(Ardashnikov Courtesy *Journal of Hygiene*)

such processes are similar but the deviation from normal is less in the case of leukemic tissue The admirable review of Kirschbaum ■ ■ concluded with the rather discouraging statement that Experiments on the genesis and therapy of mouse leukemia have thus far yielded no suggestion for improving methods of early diagnosis or treatment of the human disease" From the data which have been accumulated in regard to certain phases of the disease and the method of producing it unfailingly however it does not seem to me to be too rash to state that the work of the past few decades in this direction may serve as foundation stones for the development of a more favorable form of treatment and perhaps for a clearer understanding of the underlying cause of the disease

In addition to the excellent review of Kirschbaum (57) other general articles dealing with the subject of spontaneous and experimental leukemia have been presented by Engelbreth Holm (54) Forkner C E (60) Furth (52) Richter M N and MacDowell C E (61) Richter M N (62) and Watson C J (63)

The Hereditary Factor in the Etiology—The fact that the susceptibility to experimental leukemia and the transmission of the spontaneous disease follows definite genetic laws in experimental animals causes one to consider that in humans the hereditary element might be of importance Clinical experience provides some support for this view A comprehensive study has been made by Hogreffe (64) in which he observes the frequency of age distribution of mice that die from leukemia in the different generations of a cross between the AKA line of mice with 63 per cent leukemia and the resistant II strain He concluded that these observations supported the view that the inheritance of the disease in this cross is dependent on one single dominant gene Furthermore he thought transplantation experiments demonstrated that the resulting disease has features that are in part dependent upon hereditary factors Studies by Kemp (65) lead him to believe that the development of leukemia and cancer is probably due to a common hereditary predisposition When this was written I had a young man 37 years of age under

of interest to note and possibly of importance from the standpoint of future treatment that immunity to transplanted leukemia may be accomplished by various means. Among these are the inoculation of sublethal doses of cells, injections of suspension of normal tissue cells of certain genetic constitution, the administration of heat killed leukemic cells, ultracentrifuged leukemic cell extracts, or normal defibrinated blood. Furthermore, immunity has been conferred passively by the inoculation of liver and spleen of immune animals. According to Kirschbaum it has not been possible to immunize against either the spontaneous disease or the cells of a spontaneous case of leukemia.

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tives in which there was a known case of leukemia was 17 times as great as in the control group. Furthermore in the families of patients with leukemia he estimated there was a cancer risk of 31 per cent, whereas in the population at large it is considered to be 20 per cent. It is of interest to note that this observer in addition to noting that other cases of leukemia occurred in the relatives of patients with leukemia found that it was not always of the same type for example a patient might have myelogenous leukemia and the relative be afflicted with chronic lymphatic leukemia. In summary Videbaek believes from his study and a survey of the literature that 1 hereditary factors play a role in the etiology of leukemia in humans 2 that multiple occurrence of leukemia in a family group is not always of the same type and hence that leukemia genetically is a morbid entity and 3 that as the cancer incidence in leukemic families is apparently greater than the cancer risk at large there is an inherited gene common to all forms of cancer and that possibly external influences determine the type of neoplasm which develops. Leukemia he concludes is a matter of chromosomal inheritance he does not believe it is transmitted as such but as an inherited disposition to the disorder.

The interesting suggestion is made by Ardashnikov (*70*) that some of the relatives of patients with proven leukemia may manifest evidence of the disease in the form of a lymphocytic reaction associated in particular with infection. The cases cited however although they did have a lymphocytic reaction suggested the possibility that this might have been on the basis of infectious mononucleosis. Thus a coincidental association may have accounted for the occurrence rather than accepting it as due to the influence of the leukemia genotype.

Congenital Leukemia.—Two cases of congenital leukemia are reported by Cross (*71*). One occurred in a male infant, three months of age who had the characteristic blood findings of myelogenous leukemia. Roentgen ray therapy caused a moderate decrease in the white blood cell count but death occurred a few days later. The second patient an infant one and one half months of age was also observed to have the characteristic blood findings of myelogenous leukemia. In both patients necropsy findings confirmed the clinical diagnosis of myelogenous leukemia. A review of the literature of the past 25 years by Cross (*71*) revealed that 20 cases of congenital leukemia have been reported of which 16 were myelogenous three were lymphogenous and one was questionable in type. However it does not appear possible to accept the known facts as convincing evidence that a true congenital leukemia does occur as a fortuitous association cannot be eliminated.

The Relation of Urinary Extracts to the Experimental Production of the Disease.—The experiments reported in 1939 by Wearn, Miller, and Heinle (*72*) are of interest in relation to the etiology of leukemia as new facts have been discovered which may have a bearing on the now obscure cause of the disease and perhaps lead to a new type of therapy. They

my care who was *suffering from subleukemic myelogenous leukemia* Four weeks previously his younger sister age 15 died of subacute histio monocytic leukemia while a patient on my service at the University Hospital It does not seem likely that the occurrence of more than one case of a rare disease in a blood relative is due to chance alone

The literature *bearing on this subject* has been reviewed by Ardash nikov (*66*) in which he lists 31 instances in which another case has occurred in a family The distribution according to the type of leukemia is given in Table XXXIII

It is pointed out by the author that the ratio of familial cases with lymphatic leukemia to those with myeloid leukemia 6 1 *is significant* and lends support to the idea that the association is not due to coincidence It is concluded by Ardashnikov (*66*) that in some cases at least heredi tary factors play a role in the etiology of leukemia in man According to him the most probable explanation is a conditionally dominant type of inheritance associated with the ordinary paired chromosomes especially in the lymphatic form of leukemia with great variation in the fully de veloped disease due to other genes or to external influences

The occurrence of leukemia in three sisters is reported by Hornbaker (*67*) In two of the sisters it was the lymphatic type and in the third the myelogenous variety He refers to the report of Decastello (*68*) in which in one family there were six cases of lymphatic leukemia in two generations Out of five brothers and sisters in the first generation three died of leukemia Of the nine members in the next generation three died of leukemia all of them being children of two of the three members of the previous generation who died of the disease An example of acute leukemia occurring in fraternal twins at the ages of 18 and 24 months with a review of the literature on familial leukemia is reported by Cook (*68A*) It is the opinion of Hornbaker that at the present time there is insufficient evidence to explain the occurrence of familial leukemia on the basis of heredity except for the known hereditary factor in cancer of which leukemia is now regarded by many as an example

It has not been possible in the past to prove the importance of heredi tary factors in man due mainly to the lack of sufficient and reliable con trolled data The occurrence of multiple cases in relatives and successive generations has suggested strongly however that hereditary influences in man as in animals play an important role in the production of the disorder Recently Aage Videbaek (*69*) has collected data which indi cate in a convincing manner that heredity does play a significant role in the etiology of leukemia and furthermore that the disease is related to cancer genetically In a study of 209 cases of leukemia with 4041 rela tives he found 17 cases of leukemia in the latter group whereas in the control group of comparable ages and sex distribution only one case was detected The incidence therefore of leukemia in the group of rela

filter and hence is free from cells. Furthermore from a clinical standpoint there are certain features such as fever and the increase in the white blood cell count which resemble an infection. Moreover frequently in leukemia especially in the acute varieties there is a severe infection of the mouth and throat and in some patients bacteria can be cultured from the blood stream. The evidence indicates however that these micro-organisms are present in the role of secondary invaders rather than as the primary etiologic agents. On the other hand leukemia has not been produced in animals by any organism isolated from a patient with the disease there is no evidence to indicate that it is transmissible from man to man and there is no convincing proof that it can be transmitted from a mother who has the disease to the fetus.

Attempts to transmit human leukemia from man to man with blood cellular material and from the spleen and lymph nodes has not been accomplished by the experiments of Thiersch (74). This investigator attempted unsuccessfully the transmission of acute leukemia from man to man with blood cellular emulsions from spleen and lymph nodes by subcutaneous and intravenous inoculation (74) with a subsequent observation period of 24 months. Later (75) the sternal marrow route was used. Five cubic centimeters of cellular sternal marrow was aspirated from patients with acute leukemia and this was injected through the already inserted needles into the sternal marrow of recipients within a few seconds and without any anticoagulant. Each recipient received a possible 1.5 cc of leukemic bone marrow. In three recipients all of whom were suffering from cancer either of the lip or of the tongue there was no evidence of leukemia having been acquired following these injections at the end of 21 months in two cases and at the end of 101 days in the third patient. The latter succumbed at this time with a recurrent carcinoma and aspirative pneumonia. The failure to transmit the disease is explained by Thiersch as possibly due to several factors such as the different genetic structures of the recipient from the donor the age group of the recipients their state of nutrition and the immunity to the implants due to the presence of cancer. He also suggests the possibility that the incubation period may be extremely long in leukemia and perhaps a more extended period of observation would have given positive results. It was his conclusion however that acute untreated human leukemia could not be transmitted with cellular sternal marrow by the sternal marrow route from man to man.

By direct artery to artery cross transfusion blood from leukemic patients has been transferred into non leukemic subjects. By this method it has been possible to transfuse 6 to 10 liters of blood per hour both to and from the donor and recipient. No evidence of leukemia has been observed in any recipient. The exact period of observation following such cross transfusion experiments is not stated (76).

observed that urine from patients with chronic myeloid leukemia contains some substance which is capable of producing myeloid hyperplasia and metaplasia in guinea pigs Extracts of urine from persons not having myeloid leukemia do not produce a similar change with as great a frequency They were not able to detect however any differences between the results obtained with lymphoid leukemia urine extracts and normal urine extracts The substance which produced the myeloid reaction has not been identified It is however recovered by the same methods which are capable of obtaining certain of the products of the glands of internal secretion from urine Androgens estrogens the adrenal cortical hormone and pituitary substances can be recovered by one or more of the methods employed These authors are unable to state at present whether the substance is a normal metabolic product present in excess in the urine or whether it is an abnormal product not normally present in urine If it is in excess of a normal substance it is their opinion that this may result from over production of the substance or to a decreased production of some normal neutralizing substance

More recently Miller and Turner (73) have suggested that there are *two substances involved in producing these specific histologic changes in* guinea pigs following the injections of extracts from the urine of patients with either myeloid and lymphoid leukemia One they regard as producing myeloid proliferation and the other lymphoid They suggest that the substances are mutually reciprocal in action That one stimulates myelopoiesis namely proliferation without maturation The maturation of the myeloid cells is brought about by the action of the lymphoid substance which inhibits the proliferation of the myeloid cells and hence allows them to maturate The lymphoid substance therefore brings about proliferation of the myeloid cells without maturation Maturation of these cells is produced by the action of the myeloid substance which inhibits the proliferation of the lymphocytes and hence allows them to mature Normally it is postulated that these two substances are balanced in action *and therefore regulated hematopoiesis occurs* A theory regarding the cause of myeloid leukemia is presented as follows it is considered that an excess of myeloid material occurs in chronic myelogenous leukemia together with at least a normal amount of lymphoid substance Hence the disease runs its course with greater than normal maturation of myeloid cells in evidence As the lymphoid substance becomes exhausted an acute exacerbation occurs characterized by proliferation of myeloid cells without maturation Chronic lymphoid leukemia according to their belief may be explained in a similar manner

The Relation of Infection to the Cause of Leukemia —*A small minority* of investigators still regard the condition as due to an infection and are unwilling to accept the opinion that the leukemias are neoplastic diseases This view is based largely on the fact that the disorder can be transmitted *to* fowls by a filtrate which has been passed through a Berkefeld

TABLE XXXIV

WEIGHT OF ADULT SPLEEN ACCORDING TO TYPE OF LEUKEMIA

Type of Leukemia	*Weight Range (Gm.)*	*Average Weight (Gm.)*
Acute Lymphatic	130 to 920	368
Chronic Lymphatic	100 to 4400	618
Acute Myelogenous	86 to 1650	428
Chronic Myelogenous	160 to 4930	1696
Monocytic	160 to 550	333

(Krumbhaar and Stengel. Courtesy *Archives of Pathology*.)

listed as radiologists was 3.9 per cent, which is more than eight times as great as the incidence (0.44 per cent) among those not listed as radiologists. This observer believes that this rather striking difference is substantial evidence that exposure to x-ray is a potential cause of leukemia.

A study by March (81) on the incidence of leukemia in radiologists has been made covering a 20-year interval. He has shown that during this time leukemia has occurred more than nine times as frequently in radiologists as in non-radiological physicians. According to him there is only one chance in a billion of the observed increased incidence rate of leukemia in radiologists being coincidental. According to this author the present standard means of protection against ionizing irradiation is too difficult to employ correctly in routine work, and this incidence of increased leukemia in radiologists results from insufficient care being exercised to employ the standard means of protection against ionizing irradiation.

Pathology of Chronic Leukemia.—Regardless of the type of leukemia or whether it is acute, subacute or chronic, the following four pathological changes are characteristic of the condition, namely (1) leukemic infiltration in many organs throughout the body but especially in the bone marrow, the spleen, liver and lymph glands, (2) anemia, (3) the hemorrhagic tendency, and (4) diminished resistance to infection.

The leukemic infiltration is observed in all types of leukemia. It manifests itself by an extensive and abnormal proliferation of the myeloid, lymphoid or monocytic cells throughout the tissues of the body and usually in the blood stream. In chronic myeloid leukemia there is a replacement of the bone marrow to a variable extent, especially of the sternum and long bones with myelocytes, metamyelocytes and myeloblasts. There is usually a gross enlargement of the spleen, a fibrous thickening of the capsule, a great increase in the myeloid cells of the splenic pulp and areas of infarction in from 15 to 20 per cent of the cases. Myeloid metaplasia is commonly present in the liver, which is usually moderately enlarged.

In chronic lymphatic leukemia there is an invasion of lymphoid cells which partially or completely destroys the architecture of the lymph

In June 1949, Sweet and Wallerstein (*77*) performed a blood exchange between an eight year old patient with leukemia and a prisoner from Sing Sing Prison, who volunteered for the purpose. Over a four day period, for a total interval of 20 hours, a cross transfusion was performed in which it was estimated that 18 quarts of blood passed between their circulatory systems. The child subsequently succumbed to the leukemia but the recipient remains in good health at present. It is emphasized that the *recipient in this case was healthy and therefore more likely to* resist a successful inoculation with leukemic cells.

Relation of Acute Infection to the Etiology of Leukemia.—It is concluded by Cooke (50) on the basis of statistical analysis of the age incidence and the occurrence of infections in children with acute leukemia that acute infections form one of the factors in the production of acute leukemia. This conclusion is based on the observations that 1 the highest incidence of acute leukemia occurs in early childhood, 2, the type of its age incidence curve tends to follow the frequency of acute infections in children, and 3 some acute infection usually precedes the development of acute leukemia. While the factual data are true it is not my opinion that the conclusions for which they form a basis are necessarily correct.

Possible Relation of Repeated Exposures to the Roentgen Ray to Leukemia.—While there is no convincing proof that incriminates roentgen ray exposure to the increasing incidence of leukemia two facts concerning this agent should be kept in mind. First a large percentage of our population is subjected to roentgen ray examinations especially since the introduction of the most useful procedure of employing microfilms for the detection of pulmonary tuberculosis and extensive use of the roentgen ray for other essential diagnostic purposes. Hardly a patient enters the hospital in this country at the present time without being exposed to x rays once or many times. The great diagnostic value of such procedures cannot be questioned as undoubtedly information derived from them is lifesaving in many instances. Second it has been suggested for some years that the incidence of leukemia among roentgenologists is higher than in the population at large. In 1942 Warren and Dunlap (*78*) in their comprehensive review stated that 24 cases were found in the literature. In 1944 Henshaw and Hawkins (79) concluded that leukemia was recognized 1.7 times more frequently among physicians than among white males of the population. They emphasized that their findings are in accord with the experimental observations on animals that exposures to the roentgen rays cause an increase in the incidence of leukemia. I believe of greater significance is the report of Ulrich in 1946 (*80*) who studied over 34 000 obituary notices of physicians appearing in the *Journal of the American Medical Association* between the years 1935 and 1944. He observed that the incidence of leukemia among 205 physicians

and an anemia as a result of diminished blood formation therefore results In a few patients for some unknown reason there may be a hemolytic anemia due probably to overactivity of the spleen

Infection in Leukemia —All patients with leukemia but especially the subacute and acute types have a *diminished resistance toward infection* This is in part due to a diminution in the number of cells which exhibit normal phagocytic powers and also to the fact that patients with leukemia are incapable of developing antibodies normally probably as a result of alterations in the hematopoietic system (82 83)

Coincidentally Associated Conditions —It has been pointed out by Kirschbaum and Preuss (45) that various unrelated conditions may be present at necropsy which are only coincidentally associated Certain complications however are of interest as they are directly related to the disease In 44 instances of 123 cases observed at necropsy bronchopneumonia or lobar pneumonia was present and these conditions were not infrequently the immediate cause of death It is of interest to note that in 14 6 per cent of their cases there was evidence of hyperthyroidism and nodular goiters In 13 per cent tuberculosis was present which they do not think was remarkable as the incidence of this disease is high in autopsies in the institution with which they are associated Hydrothorax was present in 13 cases ascites in 10 cases and hydropericardium in eight cases out of the total series of 123 patients They considered that these transudates were not evidence of a separate disease but were manifestations of a leukemic process and of a disturbance of the circulation of lymph and blood which might in part be due to the pressure of enlarged lymph nodes on blood or lymph vessels Ulcerative colitis and proctitis were encountered in seven of their cases all of them being acute stem cell leukemia

It has long been known that tuberculosis may have a profound effect on the course of leukemia This subject is summarized by Jaffe (84) and by Heinle and Weir (85) The latter report a case of a 36 year old male who undoubtedly had chronic myelogenous leukemia for a period of 4¹/ years At the end of this time active tuberculosis developed which was the cause of death At necropsy there was no evidence of leukemia They suggest that it is probable that some factor produced by the infection with tuberculosis altered the course of the leukemia and caused the reticuloendothelial system to revert toward normal In reviewing the literature dealing with the association of these two diseases it is concluded by these authors that the individual cases appearing in the literature may be classified roughly as follows 1 those who have leukemia for a considerable period of time and subsequently develop tuberculosis This complication may (a) not alter the course of the leukemia (b) may modify it by diminishing the clinical and pathological signs of leukemia or (c) may cause the complete or almost complete disappearance of the clinical and pathological signs of leukemia or 2 leukemia or a

glands spleen, liver bone marrow, and other organs and tissues of the body A lymphocytic infiltration characteristically causes moderate enlargement of the spleen and there may be infarction perisplenitis and thickening of the capsule of this organ A similar change eliminates most of the fat and the normal cells from the bone marrow

Leukemic infiltrations are of importance in all types of leukemia as they do occur not only in the hematopoietic organs, but in almost any tissue of the body *Their frequency in the various organs and tissues of* the body as given by Kirschbaum and Preuss (45), is as follows (exclusive of the hematopoietic organs) kidney, 63 per cent heart 34 per cent, intestines, 13 per cent lungs 14 per cent, adrenals 12 per cent, thymus 10 per cent pancreas 7 per cent central nervous system 7 per cent, skin 4 per cent oral cavity 4 per cent genitalia 4 per cent, thyroid, 1 per cent, ribs 1 per cent and urinary bladder, 08 per cent

Nature of Leukemic Infiltration —The infiltrations which are so characteristic of the leukemic process are not clearly understood It is uncertain whether these cells originate *in in situ* or if they have been transported to an organ by the blood and hence represent a true infiltration In other words is a collection of leukemic cells in the organ due to hyperplasia of local tissue elements or does it result from multiplication of leukemic cells which are carried to the organ from the bone marrow by the blood stream? As yet this question is unsettled The fact that in mammals such as the mouse by inoculating just a few leukemic cells a leukemic process can be set up *in various organs throughout the body* until it becomes widespread is some evidence to me that the latter view is probably the true one

The Hemorrhagic Tendency —Evidence of extensive hemorrhages is commonly observed at necropsy in all forms of leukemia but they are most pronounced and invariably present *in* the more acute forms Such hemorrhages may be present in all organs and tissues of the body but they are most commonly observed *in* the skin the gastrointestinal tract the epicardium the conjunctivae and the plurae They are the result largely of a thrombocytopenic purpura which is associated with a diminution of the megakaryocytes the precursors *of the platelets in the bone* marrow Due to the leukemic infiltration of the bone marrow either with cells of the myeloid lymphocyte, or monocyte series the megakaryocytes are greatly reduced *in* number and the platelets in the peripheral blood diminished to a point where purpuric manifestations are present

The Anemia of Leukemia —*An anemia is invariably present* in all types of leukemia eventually In the acute and subacute types it develops with great rapidity whereas in the chronic types it becomes apparent much slower The anemia is usually of a normocytic normochromic type and is due almost always to an invasion of the bone marrow with encroachment on the ery*throblastic cells As a result of the* diminution in these tissues the number of red blood cells which are formed are diminished

with chronic lymphatic leukemia was observed for two years following total thyroidectomy. It was concluded that this operation did not produce any changes in the bone marrow. In the interval in which the patient was studied following the operation the red blood cell count and hemoglobin decreased appreciably and the total white blood cell count increased from 150 000 to 400 000 per cubic millimeter with no essential alteration in the blood pattern. The authors conclude that hematopoiesis in chronic lymphatic and chronic myeloid leukemia is not altered by induced myxedema.

CHRONIC MYELOGENOUS LEUKEMIA

Symptoms and Physical Signs—The onset of this condition is always insidious. Undoubtedly leukemic changes occur in the circulating blood for a considerable period of time before the patient complains of symptoms. In one of my patients a supposedly healthy chaplain of a hospital the condition was discovered when he consented to supply a drop of blood for testing a physician's newly purchased microscope and hemocytometer. His white blood cell count was found to be approximately 36 000 per cubic millimeter and many myelocytes were present. It was not until about 2½ years later however that symptoms of the malady appeared although a slight enlargement of the spleen was detected on the first examination. In another patient who complained of a mild sore throat the otolaryngologist ordered a white blood cell count because he thought that the patient might have an agranulocytosis but was very much surprised to find that the count was 25 000 per cubic millimeter and that the blood findings were typical of chronic myelogenous leukemia. The patient showed no other changes in the blood or abnormal physical signs except a moderately inflamed throat. In two other of my patients the white blood cell count has varied between 12 000 and 20 000 per cubic millimeter for over a year without obvious explanation. In one the increase was discovered during the course of a routine examination at which time the patient did not have any complaints and in the other it followed a severe but very transient upper respiratory infection. It cannot be proven that the latter two patients have leukemia of course but there is no obvious explanation for the constantly present leukocytosis. In each patient the sternal marrow is normal there are no abnormal signs on physical examination fever has never been present and the patients do not have any important complaints. These cases and others which have been reported (90) indicate clearly that the blood changes of chronic myelogenous leukemia may be discovered one or two or possibly more years before symptoms of the condition are apparent or before abnormal physical signs characteristic of the condition are present.

The earliest complaints are often those associated with the anemia and consist of weakness ease of fatigue pallor dyspnea and palpitation

leukemoid blood picture may co-exist at the time the patient is first observed with development of one of the three possibilities as given above.

The association of carcinoma and leukemia is discussed by Morrison, Feldman and Samwick (86) and two cases observed by the authors are reported in detail. One was a case of adenocarcinoma of the rectum complicated by *myeloblastic leukemia* and the other a case of chronic lymphatic leukemia in which a carcinoma of the head of the pancreas was also present. In a review of the literature they state that there does not seem to be any outstanding organ or tissue which becomes involved in a carcinomatous change in leukemia. Malignancy involving the skin, muscles, stomach, trachea, lungs, pleura, breast, ear, nose, uterus, ovaries, kidneys, peritoneum and blood vessels have been reported. It is their opinion that it is difficult to assume a casual or etiological relationship between the two conditions.

The Effect of Myxedema upon Hemopoiesis in Leukemia and Allied Disorders.—It is emphasized by Paul, Limarzi and Seed (87) that anemia is a frequent finding in myxedema and there is evidence to indicate that with absence or decreased function of the thyroid gland there is depression of erythropoiesis. Observations on the effect of diminished thyroid function on myelopoiesis and lymphopoiesis are scanty. In 1934 it was reported by Dameshek and his associates (88) that improvement occurred in a patient with chronic lymphatic leukemia following total thyroidectomy. In the following year, however, Witts (89) concluded that no clinical or hematological benefit followed thyroidectomy in a patient whom he observed.

Paul and his associates (87) did a total thyroidectomy on a patient with polycythemia rubra vera and four cases of erythroleukemia. In each instance the patient developed a myxedematous state as evidenced by a dry, coarse skin, puffiness, cold intolerance, depressed basal metabolic rate and elevated blood cholesterol. In all four of these cases there was a reduction in the red blood cell count and hemoglobin of the circulating blood. In the patient with polycythemia rubra vera the red blood cell count fell from 8,620,000 to 3,180,000 per cubic millimeter and the hemoglobin from 21.5 to 11.5 grams. The anemia was macrocytic and hyperchromic in type. Leukopoiesis was unaffected. In three cases of erythroleukemia a total thyroidectomy was followed by a moderate to marked depression of erythropoiesis. The anemia was either macrocytic or microcytic in type. Total thyroidectomy was done in one patient with chronic myelogenous leukemia and another with chronic lymphatic leukemia. Neither of these patients were affected favorably. The case of myeloid leukemia survived for one year following total thyroidectomy and except for the characteristic manifestations of myxedema there were no changes noted in the clinical or hematological picture. The patient

Cutaneous Involvement.—With the exception of purpura skin lesions are not common in chronic myelogenous leukemia. According to Epstein and MacEachern (91) the cutaneous lesions of this variety of leukemia when they do occur are just as distinctive as those found in Hodgkin's disease and lymphosarcoma. These observers report that the specific lesions occurred in 5.5 per cent of the cases in their series. It is considered by Goldhamer and Barney (92) that true myelogenous leukemia with cutaneous involvement is a relatively rare clinical entity as only 16 cases had been reported up to the time their article appeared.

The typical lesions are due to a leukemic infiltration of myeloid cells into the corium overlying the adipose tissue beneath the skin. The eruption appears as nodules varying in size from a glass headed pin to a cherry and in color from that of normal skin to a deep purple. The nodules are most frequently observed over the anterior surface of the chest and the extremities. Rarely do they occur over the face or on the mucous membranes. Usually there are no local symptoms accompanying the lesions.

One fact of considerable importance emphasized by Goldhamer and Barney (92) is the ominous significance of these lesions as regards to prognosis. They found from a survey of the reported cases, that the time between the appearance of the specific skin lesions and death varies from 11 days to four months with an average of 64 days. From these observations it can be concluded that the skin manifestations appear late in the course of the disease and their presence indicates that the expectancy of life can commonly be measured in weeks.

In addition to the specific lesions various other toxic cutaneous manifestations are not uncommonly encountered in myelogenous leukemia. According to Epstein and MacEachern (91) in their group of patients such lesions had an incidence as follows: hemorrhagic lesions 30.0 per cent, maculopapules 3.3 per cent, bullae vesicles 2.2 per cent, furunculosis 2.2 per cent and herpes zoster 1.1 per cent.

It should be kept in mind that as patients with chronic myelogenous leukemia may be treated with large doses of arsenic in the form of Fowler's solution for long periods of time some changes in the skin may be due to this drug. Arsenical poisoning produces well known cutaneous changes which may be of the nature of a diffuse erythema, macular lesions and rarely melanoderma and pustules. Occasionally there is a dull diffuse brownish red pigmentation which I observed in a patient in whom the leukemia had been benefited greatly by the drug. Being a very comely woman both she and her husband were considerably disturbed by the obvious change in her appearance. The most characteristic lesions of arsenic poisoning due to Fowler's solution are the keratoses of the skin and hyperkeratoses of the soles of the feet. Patients who take this drug in large dose should be observed constantly for these changes.

Others first experience a dull dragging pain in the region of the left upper quadrant due to the enlarged spleen or their attention may be attracted to the bulging abdomen associated with the enlargement of this organ

Additional symptoms are those arising from the increased basal metabolic rate which is frequently present in these patients These manifestations which in my experience have never been as prominent as in patients with toxic goiter consist of tolerance of cold increased sweating tachycardia loss of weight and fever

As the disease progresses the anemia and its associated symptoms become more pronounced Daily febrile rises not infrequently of considerable extent and loss of weight are likely to occur With the development of these symptoms the patient becomes extremely weak and bed rest becomes necessary Toward the end of the disease it is common to have hemorrhages into the skin and mucous membranes which are associated with a reduction of platelets in the blood stream Death usually results from an intercurrent infection or less commonly from hemorrhage into a viscus as the brain

The most characteristic findings on physical examination are the objective evidences of an anemia and the presence of an enlarged spleen The spleen in this condition is usually grossly enlarged by the time the patient consults a physician In myelogenous leukemia it is usually about three times greater in size than that of the organ in chronic lymphatic leukemia In any patient with an enormously enlarged spleen in North America the first possibility to be considered should be chronic myelogenous leukemia but in some instances such a spleen may be encountered in a patient with either chronic lymphatic leukemia or lymphosarcoma In some patients there may be no discomfort associated with the splenomegaly but it is not uncommon to have rather sharp attacks of pain in the upper left quadrant which may be associated with infarction and perisplenitis Occasionally a friction rub over the spleen may be heard It is not rare to have patients suffer considerable discomfort from a dull aching pain in the region of the spleen This may be due to the great weight of the organ or to stretching of the splenic capsule

Other physical signs are a gradually developing pallor of the skin and mucous membranes which eventually become intense as the disease progresses With this there appears evidences of loss of weight and sometimes edema of the lower extremities Characteristically there is no enlargement of the lymph nodes In an occasional patient where lymphadenopathy is observed it is usually not conspicuous or generalized In some instances when present in the cervical region it is a localized enlargement of the glands resulting from infection in the mouth or throat Occasionally however a few nodes may show a moderate increase in size due to an infiltration of myeloid cells similar to that which occurs elsewhere in the body

marrow-containing portion of bone The spongy portion is usually attacked and at necropsy it is found in various stages of absorption It is emphasized by Craver and Copeland (95) that at necropsy large areas of erosion may be found in bone which were not demonstrated in roentgen films Hence it can be concluded that the changes which are apparent roentgenologically represent relatively late alterations in the bony structure Reference should be made to the section dealing with the bone lesions in lymphatic leukemia for a discussion of the differential diagnosis and treatment of these conditions The changes in the skeleton have been reviewed recently by Snapper (96) and by Sussman (97)

It has been emphasized by Bichel (98) that in the course of leukemia in children frequently there are osteo-articular symptoms which may be so striking that they completely dominate the clinical picture In adults however such symptoms are unusual and appear in the advanced stages of the disease It should be emphasized therefore that not infrequently the joint symptoms are the initial ones and in some instances they may resemble acute rheumatic fever closely The roentgenological changes in such patients are (1) bone absorption (2) generalized osteoporosis (3) spontaneous fractures (4) periosteal layering and (5) a band of density a few millimeters wide and parallel to the epiphyseal lines Osteosclerosis has been mentioned in a few cases of leukemia in children but this must not be considered strictly leukemic in nature In some instances the roentgen picture may sometimes be normal in the presence of severe symptoms

The following patient whom I observed illustrates the importance of bony involvement in a patient with myelogenous leukemia The patient was a 44-year-old Negro male packing house worker whose chief complaint was severe and persistent pain in the back which had been present for about four months This had progressed to the point where he could not stand and when lying on his back in bed the discomfort was so intense that he could not sleep His only other complaints were fever and weakness This pain extended down the posterior aspect of both legs and the entire left leg was numb The blood picture was typical of chronic myelogenous leukemia with an elevation of the white blood cell count to over 100 000 per cubic millimeter and there was a moderately severe associated anemia The spleen was grossly enlarged Roentgen ray examination showed extensive bone destruction of the body and arch of the fifth lumbar vertebra Roentgen examination of the chest, ribs and skull showed no variations from normal Aspiration biopsy of the area disclosed large mononuclear cells which were considered to be myeloblasts Following roentgen ray therapy over the involved area, the patient s complaint of pain became much less

Changes in the Nervous System in Leukemia.—Ordinarily one does not consider that changes in the nervous system are a common or important

Involvement of Various Other Parts of the Body.—As leukemic infiltrations may be present in practically any organ or tissue of the body, the possible complications are many and are exceedingly variable in their clinical manifestations. In addition to those already mentioned the following may occur: the retinae may show hemorrhages and leukemic infiltrations; there may be destructive lesions of bone and associated pathological fracture, deafness may occur due either to hemorrhage or leukemic infiltration in the middle ear; various lesions of the nervous system may be observed which are the result either of hemorrhage, thromboses or tumor like infiltrations; hematuria associated with infiltrations of the kidneys have been encountered; myeloid changes may occur in the gastro-intestinal tract resulting in hemorrhage, but this is more likely to be observed in lymphatic leukemia.

The case of a 64 year old woman with chronic myelogenous leukemia and heart block in which improvement in the latter condition appeared to follow the therapeutic application of the roentgen ray over the heart is reported by Blotner and Sosman (93). The patient had been known to have hypertension for 20 years and leukemia for two years. For five months a 2:1 heart block had been present which was assumed to be due to a leukemic nodule or infiltration involving the bundle of His. Roentgen ray therapy applied to the cardiac area was followed by a disappearance of the heart block for several days on two occasions. On the third trial, neither the white blood cell count nor heart block was benefited by the roentgen ray treatment. Another case with granulocytic leukemia and complete heart block is reported by Dresdale, Spain and Perez Pina (94). This patient was found at necropsy to have a leukemic cell infiltration in the interventricular septum of the heart. The authors suggest that routine electrocardiograms might reveal more instances of heart block in patients with the disease.

Changes in Bone in Myelogenous Leukemia.—The changes in bone in this type of leukemia are not as common as in the lymphoid variety. According to Craver and Copeland (95) although they observed only one case (1.2 per cent) in a series of 82 patients with the disease, it is likely that the routine examination of the skeletal structures with the roentgen ray would disclose a higher incidence of involvement. The clinical course in patients in whom the bones are affected does not seem to vary importantly from the usual course of the disease.

The roentgen ray picture is characteristically one of osteoporosis or osteosclerosis with diffuse or localized areas or rarefaction. Cases with periostitis have been reported. The early lesions may be difficult to evaluate from roentgen ray standpoint and many may not be demonstrable in the roentgen films.

The pathological changes in the beginning are those of hyperplastic foci which enlarge and coalesce, eventually extending throughout the

incisions of the cavernous bodies was successful in relieving the priapism and roentgen therapy favorably influenced the leukemia

The condition may be due to nervous causes such as tabes dorsalis and injuries to the spinal cord or be present on a mechanical basis such as thrombosis hemorrhage malignant growths or inflammatory swelling and edema of the penis In 30 to 40 per cent of all cases the disorder is associated with leukemia either the chronic myelogenous or lymphatic variety or one of the acute types The disorder is often undoubtedly due to thrombosis although this may not be the only factor as Hinman (*102*) says there is a history of previous attacks in about 50 per cent of the cases Lower and Christoferson (*105*) consider that the disorder may be nervous in origin but its persistence is undoubtedly due to thrombosis in the venous spaces of the corpora cavernosa

A case of priapism due to sickle cell anemia is reported by Levant and Stept (*107*) They state that only 9 cases have been published since 1934 but it is their impression that the condition is not as rare as it appears to be Apparently it may be due to thrombosis which commonly complicates this type of anemia It is emphasized that the presence of priapism in a Negro with no other demonstrable cause should be an indication for a study of the blood for sickling

Priapism in leukemia often persists for a long period of time and may be present postmortem The treatment is the application of roentgen therapy to the penis or to localized glandular enlargement or with spray technic depending on the type of leukemia with which it is associated In other words the treatment of priapism associated with leukemia is the treatment of the underlying disease It is also the opinion of Lower and Christoferson (*105*) that roentgen irradiation of the proper type for the leukemia and also applied locally for the relief of the priapism is the treatment of choice Although prompt relief may be afforded by roentgen therapy in most cases this is followed by impotence which may be permanent or persist for a few months

In summary then it may be said that persistent and prolonged priapism should suggest the possibility of an underlying blood dyscrasia usually leukemia although it has also been reported in sickle cell anemia Treatment in the form of aspiration of the corpora cavernosa has been employed and incision of this part of the penis In leukemia however probably the most satisfactory course to follow is the general treatment of the underlying condition although local irradiation of the penis has been reported as causing improvement Relief is often obtained but impotence either temporary or permanent may follow

The Basal Metabolic Rate —In untreated patients this is elevated with few exceptions above normal limits although in some instances the increase is slight No other afebrile disease with the exception of toxic goiter exhibits such a constant abnormal increase in heat production by

complication of leukemia but the study and review of the literature by Schwab and Wiess (99) indicate that this is not correct It is surprising to learn that the pathologic reports of Tromner and Wohlwill (100) and those of Diamond (101) show that over 90 per cent of patients with leukemia have microscopic involvement of the central nervous system Schwab and Wiess (99) estimate that only about 25 per cent of cases with histologic evidence of leukemic infiltration of the nervous system exhibit neurological signs They found from an analysis of 334 cases of leukemia in Boston that 20 5 per cent of the cases had neurologic signs excluding retinal lesions The frequency of neurologic complications in the acute and chronic types of leukemias and in the lymphatic and myelogenous types were about the same In their experience the most frequently observed neurological manifestations were bilateral palsies of the seventh and sixth nerves with less frequent involvement of the fifth eighth ninth tenth, eleventh and twelfth nerves In addition they noted absent deep reflexes pyramidal tract signs paraesthesias and evidences of meningeal irritation In 73 6 per cent of the 34 patients in whom lumbar puncture was done the spinal fluid was abnormal as indicated by an increased cell count, by an increase in protein content and by an elevated pressure

Priapism —Although this condition has been mentioned frequently as a complication of leukemia it has been encountered only rarely in my experience In a comprehensive review of the literature and a general discussion of the disorder and its etiology symptomatology treatment and prognosis, Hinman (102) defines the condition as a prolonged and persistent usually painful erection which is unaccompanied with a sexual desire It is not to be confused with transitory nocturnal forms of recurrent erection which are not uncommon in inflammatory conditions of the genito urinary tract and which are usually of slight importance and are amenable to treatment Warthin (103) reports the occurrence of three cases in a period of nine years in patients with myelogenous leukemia which persisted postmortem This author believes that it is not as rare as commonly thought and considers that evidence of the condition would be obtained more often if it were sought It is the opinion of Craver (104) that the disorder is rare and he states that its frequency is exaggerated In 309 males with leukemia seen in the Crile Clinic Lower and Christoferson (105) observed priapism in only two patients This represents an incidence of 0 65 per cent of all patients with leukemia and one of 3 2 per cent in those with the myelogenous type

The condition may occur at any time during the course of the disease and may even be the initial symptom Recently the case of a boy 14 years old has been reported by Borjas (106) who had fever and loss of weight over a period of six months followed by acute priapism and retention of urine Medical treatment including antispasmodics hypnotics opiates and spinal anesthesia failed Surgical treatment in the form of bilateral

sation of warmth tolerance of cold loss of weight despite a good appetite are present to some extent in patients with myelogenous leukemia they are much less pronounced than in patients with toxic goiter who have the same rate of elevation of the basal metabolic rate This may be explained on the basis of observations made by *Briard McClintock and Baldridge (110)* which indicate that there is economy of muscular movement in patients with leukemia as contrasted with an extravagance in muscular activity in patients with exophthalmic goiter

From a practical standpoint estimations of the basal metabolic rate are not commonly employed at present as a measure upon which to base the prognosis or as an indication for treatment This is because the prognosis can usually be determined with accuracy on the basis of other information and the indications for treatment are likewise apparent from data *obtained from the examination of the blood and other clinical information* Nevertheless it is probably true that the basal metabolic rate determination should be used more extensively as an indication of the prognosis and guide to treatment

Blood Examination —Three characteristic changes occur in the typical cases They are 1 a moderately severe anemia 2 a striking increase in the total number of white blood cells and 3 a large increase in the percentage of polymorphonuclear leukocytes and the presence of immature granulocytes

The *anemia* is usually of the normocytic or slightly macrocytic type and is also normochromic Ordinarily the mean corpuscular volume is between 95 and 105 cubic microns and the mean corpuscular hemoglobin concentration 30 per cent or higher with a saturation index of 0 9 or above The color index is commonly found to be in the vicinity of 1 0 The red blood cells generally show some degree of anisocytosis and poikilocytosis and a variable number of immature erythrocytes may be present in the form of cells with diffuse and punctate basophilia nucleated red blood cells and reticulocytes In some instances where there has been excessive hemorrhage (which is usually associated with a secondary thrombocytopenic purpura the red blood cells may be smaller than normal in association with an anemia of the hypochromic type This is uncommon in the chronic variety of the disease but it may be seen in acute exacerbations of the condition

In the early *stages of the disease the red blood cell count and* hemoglobin percentage are within normal limits but by the time the patient consults a physician a moderate anemia is usually present The red blood cell count at such a time is usually between 2 5 and 3 5 per cubic millimeter In general it may be said that the degree of the anemia is an excellent index of the general status of the patient All are in agreement that the level of the red blood cell count is a better index of the patient s general condition than is the total white blood cell count

the body. In a study (*108*) of the basal metabolic rate in this disease which I made some years ago in association with Matthew C. Riddle in which 272 basal metabolic rate determinations were made on 36 patients with chronic myelogenous leukemia, the following observations were made. Of the total number of determinations 46.1 per cent were within normal limits, 1.5 per cent were minus 10 per cent or below, and 52.4 per cent were plus 10 per cent or above. In only 17.2 per cent was the metabolism elevated above +30. The high percentage of low figures in this series of patients was undoubtedly due to the fact that many of the estimations were made following intensive roentgen ray therapy and at a time when the patients had been without symptoms for some weeks. Untreated patients showed without exception an elevation of the basal metabolic rate above +10 and the majority of such determinations were between +20 and +30. The highest rate was +81.

It is obvious therefore that the relation of treatment to the height of the basal metabolic rate is important. Therapeutic irradiation of patients commonly produces a transient rise in the basal metabolic rate but usually not persisting for more than three days. In those who are benefited by the treatment this rise is followed by a rapid fall to normal where it usually remains for from three to six months and in some instances even longer. Patients who are in the terminal stages of the disease however continue to have an elevated metabolism despite therapy.

The cause of the elevation in the basal metabolic rate is not clear. The studies of Baldridge and Barer (*109*) suggest that the increased heat production is due to an accelerated protein metabolism. There appears to be some correlation with the level of the white blood cell count because the basal metabolic rate is frequently high when the white blood cell count is elevated and low with low white blood cell counts. It should be noted, however, that the immaturity of the white blood cells bears some relationship to the level of the basal metabolic rate, for when the percentage of immature white blood cells is great the basal metabolism is usually high. There does not appear to be any relationship between the basal metabolic rate and the degree of anemia. In general therefore it can be said that the level of the basal metabolic rate in untreated patients parallels roughly the degree of elevation of the white blood cell count and of the percentage of immature myeloid cells. It can be concluded from this that the height of elevation of the basal metabolic rate is a measure of the severity of the leukemic process and therefore is of value from the standpoint of prognosis and as an indication for therapy.

There is a definite correlation between the pulse rate and elevation of the basal metabolic rate in patients with leukemia as is observed in patients with toxic goiter although the pulse rate is relatively lower in the former. The other clinical symptoms and signs of an increase in the basal metabolism are not conspicuous. While a tendency to sweat easily, a sen

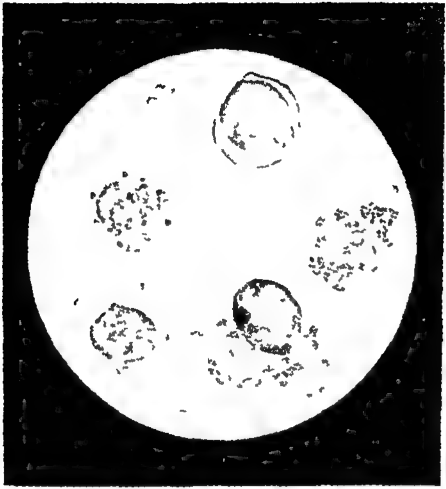

PLATE IV *Chronic Myelogenous Leukemia*—A stained blood film from a patient with a moderately advanced stage of the disease in whom the leukocyte count was 225 000 per cubic millimeter Identified clockwise from the top the nucleated cells are (1) myeloblast with several large nucleoli light evenly stained chromatin and deep blue cytoplasm without granules (2) basophilic myelocyte (3) megakarocyte (4) atypical myelocyte (5) atypical eosinophil with a few basophilic granules Wright's stain Magnification 960

In rare instances, the anemia which is present in patients with myelogenous leukemia may have the characteristic of a *hemolytic variety* with increased fragility to hypotonic salt solution and spherocytosis of the erythrocytes. Occasionally this condition may simulate true chronic hemolytic anemia in many respects. In one such case observed by me some years ago, in which all of the features of a hemolytic anemia were present, splenectomy which was performed on the basis of an erroneous diagnosis did not result in improvement. In some instances this procedure has been reported as beneficial (*111*). The subject has been reviewed by Jonsson, Hansen-Pruss and Rundles (*112*) who report a patient with chronic myelogenous leukemia and evidence of increased blood destruction. After the anemia had persisted for 11 months despite 49 blood transfusions splenectomy was performed. The hemolysis subsided and the patient's health remained good for the subsequent period of observation which was 30 months. In a series of 326 splenectomies reported by Doan (*113*) 13 or about 4 per cent were done in patients with leukemia. These were performed on the basis that the patients had *hypersplenism*, a term introduced by John H. King in 1914, and a condition emphasized especially by Doan and his associates since 1935 (*113, 114*). It is their belief that the spleen in leukemia and other conditions may develop a hyperfunction with the consequent destruction of blood cells. In some instances they conclude this may be a selective action having an effect only on the erythrocytes.

A pronounced *leukocytosis* is almost always present in patients with the chronic form of the disease. In the fully developed state the white blood cell count most frequently averages between 50 000 and 300 000 per cubic millimeter, although counts as high as 1 000 000 per cubic millimeter or even higher have been recorded. In some instances the total white count may be normal or below normal. This variety of the disease is known as subleukemic leukemia and will be considered under that section.

As many as 90 to 95 per cent of all of the white blood cells may be of the granulocyte variety. Neutrophilic myelocytes vary from a few per cent to as high as 30 to 40 per cent, whereas basophilic and eosinophilic myelocytes are usually present in much smaller numbers. Myeloblasts are frequently present but ordinarily do not make up more than 1 to 3 per cent of all white blood cells in the peripheral blood in the chronic variety of the disease. Basophilic leukocytes may be increased in number up to 20 per cent or more. It is recognized that they are more numerous in myelogenous leukemia than in any other disease. The lymphocytes may be somewhat increased in absolute numbers but their percentage is always low. Likewise the monocytes may also be increased in absolute numbers but become diminished as the disease progresses. In some instances there may be such a great increase in the eosinophils or basophils that the terms eosinophilic and basophilic leukemia have been applied.

TABLE XXXV

L.C.N NO 537821 CHRONIC MYELOGENOUS LEUKEMIA

Day	W B C	R B C	HB	Weight	Treatment
1	120 000	3 2	52	107	
2					500 cc
4					500 cc
5	85 000	4 1	75		
7–12					X Ray 700 R (Spleen)
49	5 250	4 0	77	101	(6 days)
77 Day Interval					

(2) L C N NO 53 821

Day	W B C	R B C	HB	Weight	Treatment
(126)					
1	70 000	3 4	67	112	
2–8					X Ray 70 R (Spray)
9	44 750	3 4	68	113	(6 days)
32	_0 500	4 0	80		
73	31 500	4 2	80	114	

Female 41 yrs 14 months ago symptom of anemia Splenomegaly R B C 3 2 HB 5_ W B C 120 000 P M N 81 Metamyelocytes 25% Myelocytes 16% Myeloblasts 1% Eosinophils 10% Basophils 1 L L. 3% S L. 4%

TABLE XXXV —The effects of different methods of treatment with the roentgen ray in a patient with chronic myelogenous leukemia are shown This patient a female age 41 years had experienced the symptoms of anemia for 14 months When first observed as indicated by the first set of figures her white blood cell count was 120 000 per cubic millimeter Following two blood transfusions she was given from 110 to 120 R daily for six days over the several aspects of the spleen She suffered anorexia and moderate nausea and vomiting from these treatments At the end of 37 days after treatment the red blood cell count had actually declined probably as the result of the exposure to the roentgen rays Furthermore the weight had decreased from 107 to 101 pounds In the second series of treatments 126 days later she was given 70 R with the spray technic in the form of three exposures of about 20 to 25 R each every other day There was no unfavorable reaction at any time and the results attained were better than with the former therapy This is shown by the actual increase in the red blood cell count and the gain in body weight The spray method is superior in the treatment of the chronic leukemias because it does not cause untoward reactions nor is a deleterious effect exerted on the red blood cells

The blood platelets in chronic myelocytic leukemia are usually normal or increased in number early in the course of the disease As the condition progresses they may become reduced in number and it is not rare to observe a secondary thrombocytopenic purpura when the disease is advanced In such a stage the number of platelets may be greatly diminished or practically absent from the blood stream It is usually considered a good prognostic sign when the platelet count rises after it has been at a low level A persistently low count is regarded as an unfavorable indication

patient the persistence of fever, the level of the basal metabolic rate the percentage of cells in the peripheral blood which are immature the severity of the anemia and the presence or absence of a hemorrhagic tendency One may gain a fair idea of the prognosis merely from the general appearance of the patient Of greatest importance is the evidence of loss of weight and pallor both of which are indicative of the seriousness of the disease Furthermore the persistence of a high or even a moderate fever and the failure of an elevated basal metabolic rate to return to normal following therapy are both strongly suggestive indications that the activity of the process is great and that the outlook is poor

In general it may be said that the level of the white blood cell count when considered alone does not necessarily bear any relation to the prognosis in any given case In patients with extremely high counts the outlook may be better than in those with moderate or relatively low ones provided other findings which are to be discussed later are not present It should be stated however that in patients with a total white blood cell count which is below 20 000 per cubic millimeter the possibility that improvement may follow the use of irradiation is less because the prompt drop in the leukocyte count following the application of a few treatments will contraindicate the further use of this therapeutic agent

In general it may be stated that the rapidity of the fall in the total leukocyte count following irradiation is of importance from the standpoint of the future course of the disease Although the prognosis should never be based upon a single finding it can be said that in my experience patients who have shown a rapid drop in the total white count following irradiation regardless of the level of the initial leukocyte count have had a less favorable subsequent course

There is a definite relationship between the percentage of immature cells and the outlook for life In general it may be said that when the immature cells are greater than 33 per cent of normal then the outlook is less favorable This becomes progressively so as the percentage of immature cells increases Furthermore the greater the immaturity of the cells the less favorable the prognosis For example the presence of more than an occasional myeloblast in the peripheral blood suggests a more ominous prognosis

The level of the red blood cell count and the hemoglobin of the circulating blood bear an important relationship to the prognosis It is usually true that once the red blood cell count falls below 3 0 per cubic millimeter and the hemoglobin below 60 per cent the prognosis becomes more serious With an erythrocyte count below 1 0 million it is rare for the patient to survive for many weeks although with repeated transfusions the duration of life may be lengthened appreciably It is also true that in the presence of many immature red blood cells such as normoblasts and cells with diffuse and punctate basophilia the outlook

Prognosis —There are no authentic cases on record in which a patient with myelogenous leukemia has recovered, although some have survived for a period of over 10 years. In the past it has been generally accepted that the average duration of life is between $2^1/_2$ and $3^1/_2$ years after the symptoms appear and that irradiation will prolong life on the average of six months at the most.

In individual cases, however, either this therapeutic agent is more effective or the natural course of the disease is longer, for some patients' survival period may be much longer. Although the duration of life after the appearance of symptoms is comparatively short in the average patient with the disease, over 10 per cent of the cases live for a period of five to 10 years after initial symptoms appear and instances have been reported of patients who have survived for as long as 16 years. In a series observed by Hoffman and Craver *(115)* four lived for unusual periods of time as indicated by survival periods of 16.5, 16, 12.5 and 11 years respectively.

The accumulating evidence, however, suggests that the more effective use of the roentgen ray, radioactive phosphorus, blood transfusions, and antibiotics not only control the symptoms better but prolong the life of the patient. For example, Lawrence and his associates *(116)* have shown that of 129 patients with chronic myelogenous leukemia treated with radioactive phosphorus (P^{32}) alone or in combination with x ray, the average duration of life from the onset of symptoms was 3.7 years with 21 patients still living. Of this group 24 per cent lived for five years or more and 10 per cent for eight years or longer. There have been patients with chronic myelogenous leukemia who have lived from nine to 19 years after the onset of symptoms; records of such patients have been collected by Moffitt and Lawrence *(117)*. A summary prepared by them shows that patients have survived myelogenous leukemia for periods of 9, 10, 12.5, 13, 16, 16, 16.5, 18 and 19 years respectively. They estimate from a survey of the literature that from 7 to 10 per cent of patients with chronic myelogenous leukemia may experience spontaneous remissions.

In a group of patients with chronic myelogenous leukemia reported by Wintrobe and Hasenbush *(90)* it was estimated that 1.11 years elapsed between the onset of symptoms and the recognition of the disease and that the patients survived on the average for 1.68 years after the diagnosis had been made. The total duration of life, therefore, from the time symptoms appeared until the death of these patients would be equal to 2.79 years. *It is estimated by these observers that the time which elapses from the actual onset of the disease, as indicated by the earlier changes in the blood, until the symptoms of the disease appear,* varies between two to five years. When considered with other data, this would indicate that the entire course of the pathologic process in the body from its inception until the death of the patient is from 4.79 to 7.79 years.

The outlook in any given patient is based upon a number of factors. These include the duration of the disease, the general condition of the

The lymph glands are most frequently enlarged in the cervical, axillary, and inguinal regions. They vary in size from a pea to a hen's egg and are non tender, smooth, moderately firm and not adherent to each other or the surrounding structures. Usually they increase slowly in size until exposed to roentgen ray therapy, following which they are reduced promptly. Recurrences respond to further x ray treatment but these become less effective with each application and eventually the patient becomes refractory to this form of therapy. It is not common to have them diminish in size spontaneously although it has been claimed that this may occur subsequent to an intercurrent infection. Never have I seen such glands soften and form a draining sinus unless tuberculosis has been present as a complication, which is exceedingly rare. Roentgenograms may show enlargement of the mediastinal glands and in some instances it is possible to palpate grossly enlarged glands of the abdomen. Some cases have been reported in which it has been said that there has not been enlargement of the peripheral lymph nodes throughout the course of the disease. This may be true occasionally early in the illness but I have never observed a continued absence of enlarged glands from the beginning to the end of the patient's illness.

The *spleen* in chronic lymphatic leukemia is usually moderately enlarged. As a rule it extends about three finger breadths below the left costal margin where the rounded edge is often felt, which is smooth and non tender. Rarely does this viscus attain the size commonly observed in chronic myelogenous leukemia but occasionally that is the case in the terminal phase of lymphatic leukemia in which the course has been prolonged.

The Cutaneous Manifestations of Lymphatic Leukemia.—It is recognized that the same type of cutaneous manifestations may occur in lymphatic leukemia and other closely allied conditions such as Hodgkin's disease and lymphosarcoma. There is a tendency therefore in recent years to group these conditions under the general term of lymphomas or lymphoblastomas and to describe the cutaneous manifestations in objective terms. If, for example, the characteristic blood picture of lymphatic leukemia is present in a patient with evidence of cutaneous infiltration, the diagnosis of lymphatic leukemia associated with leukemia cutis is made.

Cates (*118*) is of the opinion that in a majority of cases the cutaneous tumors of leukemia are metastatic in origin. There is, however, considerable evidence that they may originate in the skin but do not continue to be confined to it. It is her opinion that such tumors arise as the result of chance location of diffusely disseminating tumor cells. The latter, when they are once deposited in the skin, behave as independent entities and hence there is no consistent relationship between the growth of tumors in the skin and in other parts of the body.

becomes more serious In general it may be said that the severity of the anemia and the presence of immature red blood cells have the same significance from a prognostic standpoint

It is almost invariably a serious prognostic sign when the total platelet count of the peripheral blood falls to the point *where there is bleeding* from the mucous membranes and purpuric spots in the skin Although this hemorrhagic tendency may be controlled temporarily its appearance usually heralds a fatal termination often within a relatively brief period

CHRONIC LYMPHATIC LEUKEMIA

Symptoms and Signs —The onset of the illness in patients with chronic lymphatic leukemia is always insidious and the initial complaints are usually of two types namely either the patient notes the presence of a painless non tender lymph node in the neck axilla or groin or the *symptoms of an anemia are evident such as weakness ease of fatigue* pallor, dyspnea or palpitation Occasionally the patient s attention is attracted to the disease by the presence of abnormal hemorrhage from the mucous *membranes or following trauma* In *some* instances the condition has been discovered as a result of an incidental finding of a lymphocytosis during the course of a routine blood examination In such patients it may be a year or more until other evidences of the malady appear Rarely an early manifestation may be itching and *redness of the skin which is associated with a leukemic infiltration*

As the disease progresses symptoms of a progressive anemia become apparent with accentuation of pallor dyspnea palpitation and weakness There is commonly a loss of 15 to 20 pounds of body weight during the course of the disease and hence in the advanced phase of the malady the patient usually appears emaciated The lymph gland enlargement eventually becomes generalized involving the glands of the cervical axillary and inguinal regions The spleen does not frequently become *enlarged to the point where it is apparent to the patient as an obvious* bulge in the upper left quadrant of the abdomen as it does in chronic myelogenous leukemia Also in lymphatic leukemia there is less tendency than in chronic myelogenous leukemia for this organ to become infarcted and develop areas of perisplenitis with its associated pain

The commonly encountered signs on *physical examination* are associated with the anemia the enlarged lymph glands and the splenomegaly If the patient is seen early in the illness there may be no evidence of ill health *on inspection as pallor and loss of weight do not* appear until the more advanced stages In the latter stages there is moderate to extreme emaciation and striking pallor Evidences of abnormal bleeding in the form of oozing from the mucous *membranes and petechiae of the* skin are not commonly present except during acute exacerbations of the condition and as an important aspect of the terminal stage

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It is the opinion of Gates (*118*) that in leukemia there is no sharp dividing line between the so called exanthems and true tumors of the skin as the evidence indicates the unity of these two conditions which frequently cannot be separated on a pathologic or clinical basis

Epstein and MacEachern (*91*) have found it convenient to divide the cutaneous manifestations of the lymphoblastoma group into three types as follows (1) the specific lesions, (2) the toxic manifestations (leukemids) and (3) the accidentally associated lesions such as psoriasis mercury dermatitis senile angiomas and others which are of no diagnostic importance They found that, in lymphatic leukemia 46 6 per cent of their patients had some form of cutaneous involvement and that often more than one variety of change was present in the same patient Of their group of patients 8 3 per cent had specific lesions, 45 per cent had toxic manifestations and 1 6 per cent had associated lesions The specific lesions were classified as nodular, ulcerative exfoliative erythrodermia or plaques The toxic lesions in patients with lymphatic leukemia in their group occurred with the following frequency hemorrhagic lesions 25 per cent pruritis 3 3 per cent pigmentation 1 6 per cent herpes zoster 1 6 per cent maculopapular 1 6 per cent lichenoid papules furunculosis 1 6 per cent and macules 1 6 per cent

Leukemia Cutis Universalis —A rare and special form of infiltration of the skin is seen in leukemia cutis universalis which occurs most often in association with lymphatic leukemia It is regarded as an exaggerated generalized form of erythroderma due to the infiltration of tumor cells In this condition there is thickening of the entire skin which usually begins as a localized process and finally spreads to the skin of the entire body The cutaneous thickening involves the skin surface of the whole body accentuating the body folds producing a leonine appearance The swelling may be light or dark is almost always symmetrical and is accompanied by intense itching The microscopic picture is fairly constant and consists of an infiltration of small to medium sized lymphocytes a few lymphoblasts a few eosinophils and occasionally giant cells Microscopically the infiltration is observed to extend in bands throughout the cutis and in some instances into the capillary bodies The duration of the cutaneous lesions varies from a few months to several years with an average of about 2 years before it terminates fatally At necropsy there is an infiltration of the organs with lymphocytes and the other characteristic changes observed in patients with lymphatic leukemia

Mycosis Fungoides —Although this condition is most commonly associated with lymphoma such as Hodgkin s disease it may be observed in patients with lymphatic leukemia Most commonly there is a premycotic interval of several years at which time the patient has a desquamative dermatitis with pruritis At the end of this time the typical mycotic lesions occur in the form of multiple cutaneous tumors which vary in size from a pea to a child s head

Bony Changes in Lymphatic Leukemia—In a study of 86 patients with lymphatic leukemia by Craver and Copeland (95) six (7 per cent) showed changes in the bones roentgenologically. The symptoms which were not present in all patients with bony lesions consisted of pain swelling and tenderness over affected areas. The pain was usually localized and either dull or severe. The principal bones involved in the order of frequency were femur humerus pelvis skull metacarpals ulna and vertebrae. No lesions of the ribs were present in this particular group of cases. The roentgenographic picture was one of osteoclastic and osteoblastic changes and in general it could be said that osteoporosis was present in all of the involved bones.

The pathological changes in myeloid leukemia are similar to those observed in the lymphatic variety of the disorder. The process begins characteristically in hyperplastic foci which join and finally involve the entire marrow containing portion of bone. The shafts of the bone may be thinned and in some instances there may be a definite aggressive destruction of bone. (For additional discussion of the bony changes in leukemia see page 796 under the heading of Bony Changes in Myelogenous Leukemia.)

In the differential diagnosis of the bony lesions of both myelogenous and lymphatic leukemia the following conditions should be taken into consideration carcinoma multiple myeloma Hodgkin's disease lymphosarcoma and osteomyelitis. Rarely does one observe the diffuse osteoporosis found in leukemia associated with metastatic lesions which simulate an osteoplastic reaction.

It is recognized that metastatic lesions of bone are usually medullary and most frequently appear at the sites where the vessels enter or emerge from the bone. Multiple myeloma may readily be confused with the osseous changes in leukemia. The characteristic findings in the blood in leukemia the sternal puncture examination of the urine for Bence Jones bodies the elevated plasma proteins in multiple myeloma all serve to differentiate the two conditions. In Hodgkin's disease and lymphosarcoma involving bone a blood examination and biopsy of a lymph node assist in the differential diagnosis. It is known of course that in some cases of lymphosarcoma a leukemic blood picture may develop but it has now been established that the morphology of the lymphosarcoma cell is such that it can usually be distinguished from the lymphocyte seen in lymphatic leukemia. In distinguishing the bony lesions of lymphatic and myelogenous leukemia from osteomyelitis it should be remembered that periostitis is a common finding in the latter but the reaction is much more extensive and the periostitis changes give a shaggy appearance.

Treatment of the Bony Lesions—The application of roentgen ray therapy to the localized areas of bone involvement is often efficacious in relieving pain and permitting the complete repair of bone. In case the

vertebrae or other parts of the bony structure which support the body are involved various orthopedic measures such as braces and other appliances afford relief and should be employed in accordance with the needs of each individual case

Mikulicz's Syndrome.—In 1892 Johann von Mikulicz-Radecki first described (*119*) a painless bilateral swelling of the salivary and lacrimal glands which since has been called Mikulicz's syndrome. The condition is rare only one case having been observed in the 23 years that more than 1 000 patients with leukemia have been admitted to the Simpson Memorial Institute of the University of Michigan

It has a varied etiology as cases have been reported in association with *lymphatic leukemia syphilis tuberculosis and sarcoid*. The enlarged glands regardless of the etiology, show an infiltration of lymphocytes with some destruction of the parenchyma. In 1930 Rowe (*120*) reported one case from our Institute and collected 13 others all associated with definitely proven lymphatic leukemia. This author reports that the diagnosis may be made on the following points (1) painless non tender usually bilateral enlargement of any of the salivary or lacrimal glands (2) a rise in the white blood cell count with a predominance of lymphocytes among which immature forms may be seen (3) enlargement of the liver and spleen and (4) generalized swelling of the lymph nodes

The treatment of choice is the application of the roentgen ray if the condition is due to leukemia. Although temporary improvement may result, the outlook is not good as Rowe (*120*) reports that the duration of life varies from five months to five years with an average of 16 months from the onset of symptoms

Recently Hird (121) has reported a case in association with aleukemic lymphatic leukemia which responded with transient improvement following x ray therapy but succumbed 26 months after the onset of symptoms. This author concurs with the general belief that the disorder is a manifestation of a general involvement of the lymphoid *tissue rather than a* disease of the lacrimal and salivary glands

Priapism.—This rare complication may occur in any type of leukemia but it is more commonly observed in the myelogenous variety (see page 798)

Blood Examination.—It is usually possible to recognize by glancing at a blood film that a patient has chronic lymphatic leukemia. The characteristic appearance is due to the obvious increase in the total white blood count which is usually between 30 000 and 100 000 per cubic millimeter and the predominance of small lymphocytes which make up 90 per cent or more of the white blood cells present. As a result the film has a monotonous or uniform appearance because a great majority of the white blood cells resemble each other very closely. A remarkably high white blood cell count of 2 300 000 per cubic millimeter most of which were

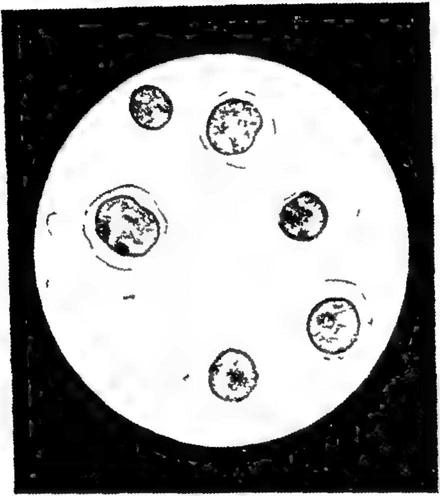

PLATE X *Chronic Lymphocytic Leukemia*—The course of the disease in the patient from whom this blood film was obtained was relatively benign, of long duration and favorably influenced by irradiation therapy. Before treatment the leukocyte count exceeded 300 000 per cubic millimeter and practically all of the cells were large or small lymphocytes showing a high degree of maturity. Note the massed chromatin of the nuclei, absence of distinct nucleoli, nuclear rim, perinuclear clear zone, and clear light staining cytoplasm containing in some instances fine granulation. Wright's stain. Magnification 960.

mature lymphocytes is reported as occurring in a patient with chronic lymphatic leukemia by Haden and Portmann (122). In most chronic cases of the disease a careful search of the blood film will disclose a few large typical lymphoblasts. In the more acute phases these cells are present in greater numbers.

In the early stages the red blood cell count and hemoglobin percentage are normal but eventually a normocytic or slightly macrocytic and normochromic anemia invariably develops. This becomes extreme as the disease progresses. In the moderately advanced states the red blood cell count is usually between 3 and 3.5 millions per cubic millimeter and the hemoglobin 60 to 70 per cent. The color index is characteristically about 1.0 unless there has been excessive bleeding which causes it to be lower. Moderate anisocytosis and poikilocytosis are commonly present. Immature red blood cells in the form of normoblasts and erythrocytes with punctate and diffuse basophilia are seen occasionally in the chronic phase of the disease but if present in considerable numbers these cells suggest that the patient is in or entering the acute stage.

The number of blood platelets is characteristically decreased to a moderate extent in chronic lymphatic leukemia although at times there may be a slight increase. This is much less however than is seen in chronic myelogenous leukemia.

The difficulty in recognizing the disease is when the white blood cell count is normal or below normal and the diagnosis from a study of the blood depends primarily upon the recognition of the immature forms of lymphocytes. This also presents considerable difficulty in the acute forms of the condition when a large percentage of the white blood cells are immature as even experienced hematologists cannot always agree on the criteria for differentiating immature lymphocytes from myeloblasts. Although the various stages through myeloblasts, myelocytes to mature polymorphonuclear cells are recognized in the granulocyte series of cells this is not true of the lymphocytes. In general the immature lymphocyte differs from the fully developed form in that the former is commonly a large cell which has a very large nucleus. This is also true of the myeloblast. In the lymphoblast the nuclear membrane is more dense than that of the myeloblast and the chromatin is coarser and may show some aggregation. Lymphoblasts generally have only one or two nucleoli and their membrane is very clear. Even with these criteria it is not always possible to identify isolated cells as lymphoblasts or myeloblasts. It must be admitted that most hematologists are influenced, and very properly so, in the recognition of the "blast" forms of immature cells by the nature of the more mature cells in any given blood film. In other words the immature cells are identified by the "company they keep."

The Basal Metabolic Rate in Patients with Lymphatic Leukemia.—The basal metabolic rate is increased in this type of leukemia as it is in

chronic myelogenous leukemia when the disease has become well established In a study of 10 patients with chronic lymphatic leukemia Friedgood (*123*) found the rate to be elevated in all of the patients The range was from +29 to +60 in seven of the 10 it was greater than +30 This observer noted that the basal pulse rate in these patients was not accelerated in proportion to the basal metabolic rate as it is in those with toxic goiter It was also observed that iodine reduced the basal metabolic rate in patients with chronic lymphatic leukemia but it did not produce the beneficial sedative effect seen in patients with exophthalmic goiter when given this drug

Prognosis —Much which has been said about the prognosis in the section on chronic myelogenous leukemia also applies to the outlook in patients with the chronic lymphatic form of the disease The two conditions resemble each other in that they are both invariably fatal diseases In general it has been stated in the past that when the period of survival is considered in a large group of patients with chronic lymphatic leukemia either treated or untreated it will be found that about two thirds of them succumb in a period between one and four years from the onset of symptoms one fifth in four to six years and one tenth in six to eight years a few die in less than a year More recently Lawrence and his associates (*124*) have reported that of 100 patients with chronic lymphatic leukemia whom they have treated with radioactive phosphorus alone or in combination with x ray the average duration of life was 4 5 years from the onset of symptoms with 24 patients still living Thirty five per cent survived more than five years and 13 per cent for eight years or more

Previously cases of lymphosarcoma cell leukemia have been included in most articles dealing with the prognosis in patients with chronic lymphatic leukemia It is thought that their presence tends to shorten the average length of life of the group For instance exclusion of these cases in our group gave an average length of life in the remaining cases of chronic lymphatic leukemia of 4 85 years instead of an average of two to three years

In our series of 86 patients with chronic lymphogenous leukemia in which the cases of lymphosarcoma cell leukemia had been carefully excluded it was found that 57 6 per cent died in one to four years after the earliest symptoms 15 per cent in four to six years 12 per cent in six to eight years and 9 per cent in nine to 10 years Twelve per cent succumbed in the first year

It was found by Wintrobe and Hasenbush (*90*) that the average time elapsing between the onset of symptoms and the recognition of the disease in his group of patients was 1 26 years The length of life after the diagnosis was made was 1 07 years which makes a total survival period averaging 2 33 years When this is considered with the fact that prob

ably the average patient with the condition has changes in the blood for a period varying between two and five years before the symptoms appear it makes the total duration of the disease from its earliest symptomless stage until the fatal termination to be between 4 33 and 7 33 years

Occasionally patients with chronic lymphatic leukemia survive for an amazing period of time I am familiar with one patient an adult male who lived for over 20 years in reasonably good health almost all of this time despite very little treatment Another instance of long survival is reported by Marlow and Bartlett (90A) They observed a male who succumbed at the age of 73 years of chronic lymphatic leukemia after undoubtedly having had the condition for 29 years It is their belief that a more optimistic viewpoint is desirable in chronic leukemia as the life expectancy may greatly exceed the average length of life as reported in large series of patients

As in patients with chronic myelogenous leukemia it is considered that unfavorable prognostic signs are evidence of loss of weight persistent fever a continuously elevated basal metabolic rate despite adequate irradiation a constantly and greatly elevated white blood cell count the presence of a considerable number of immature forms in the circulating blood an associated severe anemia and a decrease in the platelets in the blood stream which is often associated with a hemorrhagic tendency To these of course should be added the failure to respond to irradiation These unfavorable prognostic signs have been discussed in more detail in the section on Prognosis in Chronic Myelogenous Leukemia but they apply equally well here

Treatment of Chronic Leukemia—The treatment of leukemia has two important aspects (1) the use of therapeutic measures which tend to correct the results of the leukemic process as blood transfusions to combat the anemia and antibiotic therapy to control the complicating infections and (2) methods of treatment which attempt to eliminate or inhibit the underlying pathological changes as the roentgen ray radioactive phosphorus urethane folic acid antagonists nitrogen mustards and cortisone and ACTH At present these therapeutic agents while effective temporarily and often dramatically ultimately fail completely as the disease progresses and the pathological processes become refractory to them Although they may reverse the leukemic process for variable periods of time the salutary effects are always temporary and so far no form of therapy has been discovered which will either completely eradicate the malady or remain effective when administered continuously over an indefinite period of time

Roentgen Therapy of Chronic Leukemia—It is now generally agreed that two mistakes have been made in the past in the application of roentgen therapy to the treatment of chronic leukemia In the first place patients were often given excessive irradiation which resulted in severe

reactions following its use with loss of weight, fever nausea and vomiting and an adverse effect on the red blood cells and platelets Second the patients were permitted to relapse too far and consequently were in poor condition when the roentgen therapy was applied Treatment with the *small dose technique* was advocated by Dowdy and Lawrence *(125)* on the basis that (1) chronic leukemia will respond satisfactorily to smaller doses than those which have been commonly employed in the past and (2) by this *means maximum symptomatic improvement can be obtained* with minimum discomfort They did not believe that life expectancy could be altered by this treatment plan but they stated that it does result in an increased degree of comfort to the patient in comparison with therapy which employed higher individual doses of roentgen rays These authors claimed that patients with exceedingly high white blood cell counts are more comfortable if the count level of the white blood cells is

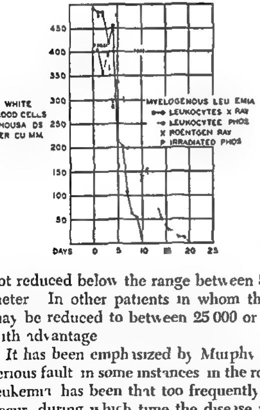

Fig 62—A prompt response to roentgen ray therapy in a patient *with chronic myelogenous leukemia* is compared to the result attained by the administration of radioactive phosphorus In both cases the initial white blood cell count was in the vicinity of 400 000 to 450 000 per cubic millimeter With each therapeutic agent the count fell to approximately normal within a period of 10 to 20 days The chart is shown to indicate that the result from these two forms of therapy produces approximately the same therapeutic effects

not reduced below the range between 50 000 and 40 000 per cubic millimeter In other patients in whom the initial count is much lower it may be reduced to between 25 000 or even 10 000 per cubic millimeter with advantage

It has been emphasized by Murphy *(126)* that the *most obvious* and serious fault in some instances in the roentgen treatment of patients with leukemia has been that too frequently serious relapses are permitted to occur during which time the disease process advances Consequently he argued the treatment is then given intensively at the time when the patient's general condition is often poor To prevent this he advised stricter observation with blood examinations routinely each month If the total white blood cell count should reach 40 000 per cubic millimeter roentgen ray treatment is administered A constant effort is made to maintain the leukocyte count as near normal as possible and never to permit it to rise *above 40 000 per cubic millimeter*

My program in the past few years for the treatment of patients with roentgen therapy has been as follows In patients with myelogenous leukemia spray irradiation is given on successive days until the white blood cell count reaches 40 000 per cubic millimeter if it has previously been greatly elevated If the white count is lower than 40 000 at the beginning and treatment is indicated for some other reason then roentgen therapy is given cautiously but ordinarily the white blood cell count is not reduced below 20 000 The spray total body irradiation technic is employed in all patients with myelogenous leukemia except in those with a grossly enlarged spleen In such patients the response is often not satisfactory and port irradiation over the spleen is indicated

In patients with chronic lymphatic leukemia port irradiation is directed toward the enlarged glands and the spleen until the desired result is obtained Occasionally the accessible lymph nodes and spleen in such patients are not enlarged and the total body irradiation technic is employed

In summary therefore our program at the present in the treatment of patients with chronic leukemia is to use total body irradiation in patients with chronic myelogenous leukemia except in those with a grossly enlarged spleen in which port irradiation is given to the spleen In patients with chronic lymphatic leukemia port irradiation is employed except in those patients in whom there is no obvious enlargement of the glands or spleen and in such patients total body irradiation is used The patients are treated before serious relapse occurs and the dosage employed is much smaller than used in previous years

The principles employed at the University of Michigan Hospital in the treatment of patients with chronic myelogenous and lymphatic leukemia are given below by Dr Isadore Lampe Professor of Roentgenology in charge of roentgen therapy who has had an extensive experience in the treatment of leukemia and allied conditions

He states The roentgen therapy methods in force at the University of Michigan which for some years have produced as satisfactory results as any reported in the literature and which are associated with slight if any unpleasant symptoms in the patients consist of two types total body irradiation (spray) and local field irradiation For both methods 200 kv radiation of H V L 1 0 mm Cu is used Total body irradiation is carried out at a distance of 225 cm and field irradiation at 50 cm

In general during recent years irradiation of the entire body has gained preference over treatment of the spleen in myelogenous leukemia and most patients are so treated today This form of treatment appears more logical in this systemic disorder but the hazard of excessive bone marrow depression is greater close clinical and hematological control is imperative Radiation is administered every other day alternating between the anterior and posterior body surfaces The daily dose will

vary from 10 to 25 roentgens (as measured in air) depending on such factors as level and rate of fall of white cell count systemic disturbance of the patient and knowledge of reaction of the patient during previous episodes of treatment White cell counts are obtained prior to each treatment The total dose is determined largely by the rate of fall of the white cell count rather than the level of the count No attempt is made to reduce the count to normal levels Irradiation of the spleen when employed is carried out using one or more fields varying in area (80 to 150 sq cm) treating daily with doses ranging approximately from 75 to 150 roentgens (as measured in air) the total dose will differ considerably from patient to patient

In lymphatic leukemia radiation is generally applied through limited areas (100–180 sq cm) to enlarged peripheral mediastinal and retroperitoneal lymph nodes and to the spleen One field is treated each day usually with a dose of 300 r (as measured in air) Most commonly this is the total dose per field nevertheless on occasion it is expedient to employ smaller daily doses protracting the treatment of an individual field over a number of days Splenic fields are never given a single dose as high as 300 r This approach serves the purpose of reducing the prominent adenopathy which is a common feature of this disease as well as to improve the hematological and clinical status of the patient When the adenopathy is not a prominent feature total body irradiation is used frequently

Indications for Roentgen Irradiation—At the time a patient reports for observation a thorough study of the presenting symptoms and signs and condition of the blood should be made for the purpose of regulating the roentgen ray treatments In general it should be emphasized that such therapy should never be administered in a routine manner depending on a set time or the level of the white blood cell count alone but only when definite indications are present Furthermore all aspects of the patient's condition should be carefully evaluated and decisions based not upon single types of information but from a careful consideration of the patient's condition as a whole In general the following are considered as indications for roentgen therapy

1 *An increase in the severity of the anemia* This is one of the most important indications for additional therapy It should be emphasized that one of the greatest problems in the treatment of leukemia is the maintenance of a reasonably normal red blood cell count and hemoglobin level If the red blood cell count falls below 4 0 million per cubic millimeter or the hemoglobin below 70 per cent (10 92 grams per 100 cc) either the administration of repeated blood transfusions or additional roentgen ray therapy or both forms of treatment should be given serious consideration

2 *The presence of symptoms of pressure or pain in the spleen* This is commonly persistent and severe causing much discomfort due to in

farction of that organ associated with areas of perisplenitis and to stretching of the splenic capsule Whatever the cause this complaint is usually alleviated promptly by roentgen ray therapy directed to this viscus

3 A progressive loss of weight which is due to an increased basal metabolic rate continuous fever and anorexia

4 Experience in recent years has shown that an increase in the total leukocyte count or of immature white blood cells in the circulating blood are indications for roentgen therapy In my opinion if the white blood cell count is greatly elevated say 100 000 to 200 000 per cubic milli meter it is always an indication for the use of x ray treatment When the level of the white cells reaches this extent in my experience rarely have symptoms been absent *Even when they are nevertheless I would treat if the white blood cell count is greatly elevated even though the symptoms are not of importance at the time* Such patients rarely are free from manifestations of the disease for any great length of time As previously stated when the white blood cell count is less than 40 000 it is my policy now to apply treatment cautiously and then not unless clear cut indica tions are present Experience of the past few years shows this is a wise policy

5 Increasing fatigue When ease of fatigue is constantly becoming more noticeable in these patients it is usually associated with a pro gressive anemia fever loss of weight and in some cases an increased basal metabolic rate Regardless of the cause it is an important symptom and clearly indicative of the need for further roentgen treatment

6 A progressive enlargement of the spleen liver lymph nodes or evidence of leukemic infiltrations in other organs Such changes indicate definitely that there is an extension of the disease process which suggests strongly the need for further therapy

7 Hemorrhagic manifestations such as purpuric areas in the skin and bleeding from mucous surfaces Such signs are ominous ones as they are usually secondary to a reduction of the platelets in the circulating blood While roentgen ray therapy is not always helpful in the presence of this complication nevertheless it should be tried for when used in combination with blood transfusions the condition may be controlled

In general it should be emphasized again that too much dependence should not be placed upon any one symptom sign or laboratory finding as a guide to therapy The decisions as to whether treatment should be given or withheld must be based upon a consideration of all of the various possible indications for treatment as outlined above and the general condition of the patient

Results from the Use of an Intensive Short Course of Roentgen Therapy—The results obtained by the use of an intensive short course of roentgen therapy in 264 cases of leukemia at the Simpson Memorial

TABLE XXXVI

RESPONSE TO INTENSIVE SHORT COURSE ROENTGEN THERAPY IN CASES OF LEUKEMIA*

	Total	Unfavorable		None		Fair		Good		Very Good		Excellent	
Type of Leukemia	*Number*	*No*	*%*	*No*	*%*	*No*	*%*	*No*	*%*	*No*	*%*	*No*	*%*
Myelocytic	104	[illegible]	0.0	2	1.9	8	7.7	38	36.5	43	41.3	13	12.5
Myeloblastic	16	5	31.3	9	56.3	2	12.5	0	0.0	0	0.0	0	0.0
Myelomonocytic (chronic)	17	0	0.0	5	29.4	5	29.4	5	29.4	2	11.8	0	0.0
Myelomonocytic (acute)	8	3	37.5	4	50.0	1	12.5	0	0.0	0	0.0	0	0.0
Histiomonocytic (chronic)	6	0	0.0	2	33.3	0	0.0	3	50.0	1	16.7	[illegible]	0.0
Histiomonocytic (acute)	1	0	0.0	1	100.0	[illegible]	0.0	0	0.0	0	0.0	0	0.0
Lymphocytic	50	0	0.0	2	4.0	6	12.0	10	20.0	13	26.0	19	38.0
Lymphosarcoma Cell	52	12	23.1	10	19.2	13	25.0	6	11.5	[illegible]	11.5	5	9.6
Lymphoblastic	10	3	30.0	4	40.0	3	30.0	0	0.0	[illegible]	0.0	0	0.0

* Unfavorable exacerbation of leukemic process with early death none course of disease apparently unaltered fair transient clinical improvement but no real remission good significant clinical and hematologic improvement lasting three to six months very good lasting six to twelve months excellent lasting more than twelve months
(Bethell Courtesy *Annals of Internal Medicine*)

Institute at the University of Michigan are given in Table XXXVI This does not represent however the most recent technic employed in the treatment of leukemia For example in patients with myelogenous leukemia the exposure was limited to the splenic area in myelogenous and the myelomonocytic types Port irradiation was given to patients with chronic lymphatic leukemia Though the technic employed had not been improved upon (see page 817) the results given below indicate what is to be expected in the way of responses of different types of leukemia to roentgen therapy With the improved technic as given on page 815 the results are superior

	Results Good or Excellent (per cent)	*Results Unfavorable or Poor (per cent)*
Chronic Myelogenous Leukemia	90.4	9.6
Chronic Lymphatic Leukemia	84.0	16.0
Chronic Histiomonocytic	66.7	33.3
Chronic Myelomonocytic	58.[illegible]	41.2
Lymphosarcoma Cell Leukemia	32.7	67.3

The results of the same type of treatment in patients with various types of acute leukemia are as follows

	Results Unfavorable or no Effect (per cent)	Results Fair (per cent)
Acute Myeloblastic Leukemia	87 6	12 4
Acute Lymphoblastic	70 0	30 0
Acute Histiomonocytic	100 0	0 0
Myelomonocytic	87 5	12 5

Inasmuch as such a large percentage of the patients with acute leukemia were not benefited or had an unfavorable result from x ray therapy and only a small group have a fair effect which is defined as "transient clinical improvement but no real remission *it appears clear that this form of therapy is of little or no use in acute leukemia and in some cases it actually has an injurious effect*

Contraindications to the Use of the Roentgen Ray —The contraindications which should be carefully considered before irradiation is employed are now well recognized As previously mentioned it is established that in acute leukemia or in an acute exacerbation of chronic leukemia roentgen ray therapy is valueless and in some cases it may do actual harm *It is tempting to be "doing something with x ray for patients in such a tragic situation but my experience is in accord with the generally accepted observation that its use on this stage of the disease is ill advised* While the presence of as many as 50 per cent of myeloblasts monoblasts or lymphoblasts is not in itself sufficient to deter treatment with the x ray it should be applied with extreme caution when such circumstances prevail and when this percentage or more of immature white blood cells are present it can be forecast that probably little benefit will result In such patients the dosage should be small and the treatments given over a considerable interim such as three times weekly or with longer intervals intervening Furthermore a daily white blood cell count and determination of the differential formula should be done If there is a precipitous fall of considerable extent in the total leukocyte count further roentgen ray treatment should be deferred

Following the appearance of a leukopenia or a hemorrhagic tendency which *arises spontaneously* the x ray *treatments should* be used with extreme care if at all for when these complications are present it is unlikely to result in improvement If either of these conditions develop during the course of roentgen therapy then they are indications to cease treatment

There is no definite level of the white blood cell count which is an absolute indication to stop roentgen ray therapy But in general it may be said that in patients in whom it is above 200 000 per cubic millimeter before treatment no further exposures should be given when the count falls below 25 000 per cubic millimeter

When the initial leukocyte count is below 20 000 per cubic millimeter before any form of treatment is applied the results of roentgen therapy

TABLE XXXVII

C M NO 498854 MALE AGE 30—MYELOGENOUS LEUKEMIA—TREATMENT WITH RADIOACTIVE PHOSPHORUS

Day	*W B C*	*R B C*	*HB*	*Weight*	*Treatment*
1	202,000	4 1	67	161	P_{32} 6 m c
16	139 000	3 6	58	162	P_{32} 6 m c
46	120 000	4 7	82	160	P_{32} 3 5 m c
66	74 000	4 9	82	163	P_{32} 6 m c
79	34 750	5 9	86	160	O
132	131 000	4 4	78	163	P_{32} 7 m c
192	239 000	4 3	71	170	P_{32} 8 m c

TABLE XXXVII —C M No 498854 a 30 year old male who had the onset of his illness three years previously when he noted hemorrhagic areas over his lower extremities Shortly after this his spleen became enlarged to the size where it attracted his attention Coincident with this he developed weakness pallor ease of fatigue and dyspnea Treatment in the form of blood transfusions and the roentgen ray did not result in improvement Following treatment with radioactive phosphorus his strength improved greatly so that he was able to return to work and to play golf Under the heading of treatment the symbol P_{32} indicates the dosage of radioactive phosphorus in millicuries

have usually been disappointing in my experience Nevertheless it may be employed with extreme caution if daily white blood cell counts are done and treatment stopped provided the count falls below 10 000 per cubic millimeter In rare instances only have I accomplished beneficial effects in the treatment of any type of leukemia with this therapeutic agent when the initial white blood cell count has been below 10 000 per cubic millimeter

The presence of a severe anemia does not contraindicate the use of the roentgen ray, but it is advisable in such patients to precede the x ray exposures with several blood transfusions and to discontinue further treatments if the anemia becomes more severe

Treatment of Chronic Leukemia with Radioactive Phosphorus —Since the introduction of radioactive phosphorus into the treatment of leukemia based on the studies of John H Lawrence and his associates begun in 1936 (*127*) a sufficient period has elapsed which permits an evaluation of this therapy This agent has been found to be highly effective in the treatment of chronic myelogenous leukemia It is of much less value in chronic lymphatic and monocytic leukemia and is contraindicated in acute leukemia It is of little or no use in lymphosarcoma and in Hodgkin s disease Opinions differ concerning its efficacy in patients with multiple myeloma but in our experience a few patients are relieved partially of pain when large doses are given It is the treatment of choice in patients with polycythemia vera

The advantages of radioactive phosphorus are its wide tissue dispersion its prolonged effect and its relatively high selective uptake by rapidly growing leukemic tissue and bone Since radioactive phosphorus which has a half life of 14 3 days emits only beta particles with a peak range in

tissues of 8 mm and an average one of approximately 2 mm and there is a selective greater uptake by leukemic tissues and bone this material possesses advantageous characteristics for the treatment of patients with myelogenous leukemia. Because the beta rays have such short penetration the patients do not suffer from radiation sickness and it is not necessary to isolate them in order to protect others with whom they come in contact. One patient of mine a college youth 19 years of age has been successfully treated as an ambulatory patient without missing any of his regular college classes

One disadvantage is the limited and variable supply which is now being corrected by the production of the larger amounts which are now made available under federal supervision to qualified physicians and institutions with the proper facilities for the handling of radioactive materials. A more serious objection to its use is the variable dosage necessary for the production of a satisfactory effect. Patients differ in their susceptibility to the action of this material and hence each one is an individual therapeutic problem. Overdosage is undesirable as there may be severe injury to the bone marrow with a sharp reduction in the blood platelets the red blood cells and granulocytes of the circulating blood

Dosage of Radioactive Phosphorus—According to Lawrence (*128*) when radioactive phosphorus is given in a soluble form either by mouth or intravenously from 60 to 80 per cent will be taken up by the body and the rate of excretion in the urine and stools is relatively slow. According to this investigator who has had a long experience with this form of treatment it has been determined that a millicurie of P[32] will deliver throughout its life in the body approximately 6 r of radiation when both the rate of excretion and decay are considered. By this means Lawrence is able to give doses of P comparable to those of x rays to leukemic patients in terms of roentgens. In their patients the dosages have varied considerably but in general they have ranged from 10 to 200 roentgens as total body irradiation. Doses of 1 to 2 millicuries may be given intravenously once or twice a week until the desired result is accomplished. In some patients as little as 5 millicuries in one of two doses will be sufficient while in others 30 or more millicuries are necessary over several weeks. In general judging from the experiences of Lawrence and his associates (*116*) patients of average size with chronic myelogenous leukemia received an average dose of 1 to 2 millicuries a week for 4 to 8 weeks or a minimum dosage of 4 millicuries in 4 weeks and a maximum one of 16 millicuries in 8 weeks. In recent years I have treated my patients with a single dose of 5 to 7 millicuries once a month until the desired result is attained. No attempt is made to bring the leukocyte count to normal. If it is greatly elevated when the count reaches the vicinity of 40 000 per cubic millimeter further medication is suspended and the patient kept under observation until the count rises appreciably above this level

Care should be exercised to avoid overtreating the patient If there is a satisfactory increase in the hemoglobin content and red blood cell count immature white blood cells are not present in excessive numbers the patient is gaining body weight and experiences an improvement in general health then the results should be accepted as satisfactory and further immediate treatment withheld

When a single dose of 5 to 7 millicuries of radioactive phosphorus is given it is estimated that a large per cent of the improvement follows within about 60 days but experience tells us that unless a satisfactory response has not been attained from a dose of 5 to 7 millicuries within four to six weeks consideration should be given to a repetition of the dose in the same size or perhaps in a somewhat larger amount

The *contraindications to the use of radioactive phosphorus* are the same as those for the roentgen ray given on page 819 In summary this form of *therapy is contraindicated in the acute leukemias in the presence of a leukopenia* or hemorrhagic tendency arising spontaneously and usually when the white blood count is below 40 000 per cubic millimeter If it is used when the white blood cell count is *less than 40 000 per cubic millimeter extreme care should be employed* and only the smaller doses injected The presence of a severe grade of anemia is an indication for the administration of a sufficient number of blood transfusions to bring the red blood *cell count and hemoglobin content of the peripheral blood to normal* before therapy is given

It has not been demonstrated that the results following the use of radioactive phosphorus in patients with chronic myelogenous leukemia are superior to the use of spray irradiation At least they are as good and the figures presented by Lawrence and his associates suggest that an efficient life may be maintained for a considerable period of time Lawrence and his collaborators believe *(116)* that Comfortable life is prolonged but state that selective irradiation provided by P^{32} has not resulted in any marked improvement in the duration of life in this disease They *emphasize however that as 33 of their 129 patients have survived for five or more years after the onset of their symptoms it is evidence that many patients with the disorder may have "many years of relatively comfortable life and it is not possible to predict which these will be when they are first seen"*

As radioactive phosphorus is regarded as acting in a manner similar to *total body irradiation it would not be expected that the results obtained from this form of treatment would be as favorable as the use of port irradiation in lymphatic leukemia* Nevertheless Lawrence and his associates (124) *have reported on the study of 100 cases of chronic lymphatic leukemia treated with radioactive phosphorus* (P^{32}) alone or in conjunction with the roentgen rays At the time of their report of the 100 patients 33 per cent of the group had lived five years or more after the onset and 10 per cent eight or more years *these figures for duration of life will be ex*

ceeded since 24 of the patients are still living They believe this method of therapy is advantageous on account of its convenience to both the patient and the physician and because there is a lack of radiation sickness

In summary it may be said that treatment of leukemia with radioactive substances is considered to be another method of administering radiation therapy and if the radioactive material is distributed over the body it is equivalent to total body irradiation and all tissues are exposed to sources of this irradiation Now that the radioactive phosphorus is available for widespread distribution to institutions and those trained in its use it is likely that it will be employed more commonly the advantages being the

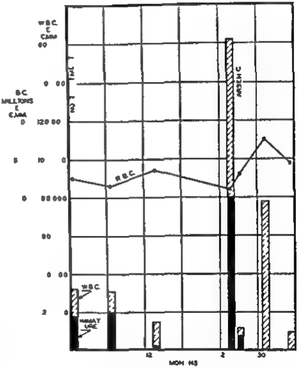

Fig 63 —Blood findings in the case of a patient 40 years of age in whom the condition was discovered when he volunteered to serve as a "normal subject for an intern to test his new hemocytometer The latter was much surprised to find that the total white blood cell count was approximately 36 000 per cubic millimeter The red blood cell count was normal The patient was entirely free from symptoms at that time but was found to have a spleen which extended about 2 fingers breadths below the left costal margin Two years later the white blood count was found to be 160 000 per cubic millimeter with many immature forms There was a very excellent temporary response to the administration of arsenic in the form of Fowler's solution Eventually the typical and complete picture of myelogenous leukemia developed The patient died approximately 4 years after the white blood cell count was found to be elevated and about two years after symptoms appeared

ease of administration and lack of systemic reactions It should be used only in the chronic types of leukemia It is unlikely that it will be beneficial in the acute forms of the disease and may even be harmful Its use in these forms of leukemia therefore is contraindicated

Arsenic —Arsenic in the form of Fowler's solution with the dosage increased to the tolerance of the patient sometimes produces satisfactory results especially in the myelogenous type of leukemia It is considered to be a protoplasmic poison and probably injures cells by acting on the

sulfhydril (SH) groupings thereby interfering with cellular oxidations If the latter is intensive enough there may be a lethal effect on cellular respiration which accounts for the inhibition of the formation of leukocytes, and the favorable action of arsenic in the leukemias The initial dosage of Fowler s solution should be 4 to 5 minims (0 25-0 3 cc) three times daily gradually increasing to an effective dose which in some instances may be as much as 40 minims daily The solution of potassium arsenate should be *given well diluted in fruit juice and must be taken immediately after meals*

There is no doubt but what arsenic in adequate doses will produce a beneficial effect in patients with chronic myelogenous leukemia On the other hand it is distinctly inferior to irradiation as a form of treatment Its results are not uniformly as good and in addition unpleasant toxic effects commonly follow its use These are most frequently nausea and in some instances severe diarrhea which result in the loss of a considerable amount of body weight In one patient recently seen by me, there had been a most striking improvement in the blood produced by the administration of 5 minims of Fowler s solution three times daily for a considerable length of time Unfortunately a rather pronounced and unsightly pigmentation had also developed which was undoubtedly due to arsenical poisoning

In general, I am not enthusiastic about the use of arsenic as a form of treatment in patients with leukemia as all will admit that it is much less satisfactory than irradiation On the other hand if the facilities for irradiation are not available or the patient no longer is benefited by the roentgen rays then it is worth while to give this type of therapy a cautious trial

Some valuable points in the therapeutic use of solution of potassium arsenite have been made by Kandel and LeRoy (*129*) These authors do not believe that arsenic and roentgen ray therapy are antagonistic They state that as soon as a postirradiation decline of the leukocyte count ceases a further remission may be induced with arsenic Also they are of the opinion that years of arsenic medication do not necessarily render a patient resistant to roentgen therapy This claim is worthy of consideration but from my own experience I have never been convinced that it is true

In my opinion however it may be worth while to consider the use of arsenic at a time when apparently the patient becomes refractory to the roentgen ray in the hope that further improvement in the patient may result This certainly does not occur in most patients because rather than being refractory to the roentgen ray the natural course of the disease is such that it has progressed to the point where *all* therapeutic agents are ineffective Nevertheless arsenic deserves a trial even under these conditions On the other hand I have seen occasional patients benefited by

roentgen ray therapy after having been treated with arsenic for a long period of time and when they have apparently reached a point when the drug is no longer effective

It is also emphasized by Kandel and LeRoy (129) that although the disease from which the patients are being treated will ultimately be fatal all effort should be made to avoid any type of therapy which will increase their discomfort They report that 5 out of 6 patients who were treated for prolonged intervals with arsenic in the form of solution of potassium arsenite the following signs of chronic inorganic arsenical poisoning developed herpes zoster keratosis cirrhosis of the liver and polyneuritis These authors emphasize that serious evidences of arsenical poisoning such as keratosis cirrhosis and neuritis may develop without the signs of the so called appearance of minor toxic manifestations as conjunctivitis nasal congestion and gastro intestinal disturbances Hence a patient should not be permitted to dose himself *according to his idea of tolerance*

It is recommended by these observers that the 21 day cycle of increasing doses of solution of potassium arsenite followed by 21 days of rest is the most satisfactory method of administering the drug Even with this plan of therapy it should be remembered that differences in the susceptibility of patients to arsenic with respect to the development of serious complications is known to vary They recommend that the soles and the palms be scrutinized carefully that the abdomen should be examined frequently for the evidences of ascites and that caution be employed when herpes zoster or parathesia appears The presence of keratoses does not mean that the drug should never be employed again in the patient but it should be discontinued until all of the soreness leaves and then it should be given again with great caution

Treatment of the Anemia in Patients with Leukemia —Eventually all patients with leukemia whether it be acute subacute or chronic in type will develop an anemia of clinical significance It is almost always myelophthisic in nature and normocytic or slightly macrocytic and normochromic in type In most patients with chronic leukemia it is usually not severe as the red blood cell count frequently varies between 2 5 to 3 0 per cubic millimeter and hemoglobin between 7 8 gm (50 per cent) and 9 3 gm (60 per cent) In the acute and subacute types the anemia often develops rapidly and may be of a severe degree Occasionally the anemia is hemolytic in nature and temporary improvement may follow splenectomy but certainly the indications for this procedure are rare and not accepted by all (see page 184)

The only treatment which is effective other than measures directed toward the control of the leukemia is blood transfusions which should be used liberally It is my policy to give them at any time the blood hemoglobin falls below 11 0 gm (70 per cent) and then to give a sufficient number to maintain the blood at this level Such transfusions in my opin

sulfhydril (SH) groupings thereby interfering with cellular oxidations If the latter is intensive enough there may be a lethal effect on cellular respiration which accounts for the inhibition of the formation of leukocytes and the favorable action of arsenic in the leukemias The initial dosage of Fowler s solution should be 4 to 5 minims (0 25-0 3 cc) three times daily gradually increasing to an effective dose which in some instances may be as much as 40 minims daily The solution of potassium arsenate should be *given well diluted in fruit juice and must be taken immediately after meals*

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may be stated from our experiences in accord with that of others that the nitrogen mustards are effective therapeutic agents in patients with various forms of lymphoma especially the generalized type of Hodgkin s disease Although it produces some benefit in patients with various varieties of chronic leukemia and in polycythemia there are other types of treatment which are superior It is contraindicated in patients with acute leukemia More recently an oral form of the nitrogen mustards Triethylene Melamine has been introduced and may be more effective in the treatment of chronic leukemia although the preparations are so new at the present time that no definite statement can be made concerning their efficacy

Urethane —In 1946 it was first reported by Paterson and her associates (*131*) that urethane (ethyl carbamate) exerted a beneficial effect in patients with myelogenous leukemia Its mode of action has been emphasized by Bastrup Madsen (*132*) who states that it is a mitotic poison which acts on dividing cells by two main mechanisms first fewer cells enter mitosis second mitosis is arrested at the metaphase In studying tissue cultures this observer also noted that the damage inflicted on the nondividing cells is not irreparable as they are capable of continuing their growth in a normal manner when removed from contact with urethane This serves as a laboratory basis for the continuation of a maintenance dosage of the drug in patients following the satisfactory induction of a remission

Clinical experience has shown that unquestionably urethane depresses the bone marrow in patients with myelogenous leukemia Moreover if the dosage is excessive there may also be a progression in the severity of the anemia with a pronounced leukopenia and thrombopenia The preparation is valueless in acute leukemia It has been reported by Loge and Rundles (*133*) that it produces beneficial effects in multiple myeloma which is now generally regarded as a subleukemic plasma cell leukemia Our results in patients with multiple myeloma have been encouraging

In many cases of chronic myelogenous leukemia the average total daily dose necessary to induce a remission is 3 0 grams This should be given in enteric coated tablets of 0 3 each One such tablet should be given three times daily until a total daily dosage of 10 tablets or 3 0 grams is reached A beneficial effect is observed usually within three weeks as evidenced by a decrease in the total white blood cell count the hemoglobin and a relief partial or complete of the patient s symptoms Once a satisfactory remission has been induced a maintenance dose of from 1 0 to 1 5 grams should be given daily It should be kept in mind that patients receiving this drug may have an excessive depression of the bone marrow and hence the preparation should be given only to patients who are cooperative and will remain under the supervision of the physician

The patients to whom this form of therapy has been given in our experience have been troubled considerably with nausea and sometimes vomit

ion are of value only because they contribute hemoglobin to the circulating blood. It is not my belief that the blood platelets or the white blood cell content of the transfused blood exerts a beneficial effect on patients with the disease. Although blood transfusions have been advised in patients who are suffering from the effects of a thrombocytopenic purpura on the basis that they may add blood platelets or as a means of resisting infections because they may add normal white blood cells, I do not consider that this is a rational basis or an indication for use of transfusions. In my opinion the use of fresh or bank blood is equally efficacious.

Treatment of Infections of the Mucous Membranes.—As has been previously stated, ulcerative lesions are likely to develop in the oral mucous membranes and throat in any patient with leukemia when the granulocytes of the circulating blood are greatly reduced in number. It is assumed that this occurs as a result of a loss of the defense mechanisms which prevents the pathogenic bacteria present on all mucous surfaces from producing ulcerative lesions. These changes are observed not only in some types of leukemia but also in agranulocytosis and aplastic anemia when the granulocytes are greatly reduced or may be entirely absent. It is most commonly seen in the acute lymphatic and monocytic varieties of leukemia.

The most effective treatment for the relief of infection in patients with leukemia is the liberal administration of antibiotic drugs. It is recommended that penicillin in doses of 1.2 to 3.0 million units or more per 24 hours be given intramuscularly. If the organisms are resistant to this antibiotic preparation, then others such as aureomycin, streptomycin or terramycin should be given a trial. A satisfactory local treatment is the use of hydrogen peroxide mouthwash, either full or half strength, as tolerated by the patient. If this type of medication proves too harsh, then an alkaline mouthwash made by the addition of a teaspoonful of sodium bicarbonate to a glass of warm water may be used. In the treatment of the swollen and inflamed gums good effects may be attained by the application of a mixture of equal parts of tincture of kino and myrrh. In some patients apparent benefit has followed the application of neoarsphenamine in glycerine.

The Use of Nitrogen Mustards in the Treatment of Leukemia.—These preparations were derived from mustard gas first employed in chemical warfare during World War I. They were first found to have a beneficial effect on neoplastic disease by Gilman and his associates (*130*) during World War II. As these preparations produced leukopenia, granulocytopenia and lymphopenia in experimental animals, it led to their introduction into medicine and a trial in leukemia and Hodgkin's disease. These preparations produced a most effective result in the lymphoma group and a further discussion of their action and indications for their use is given under the title of "Treatment of Lymphomas," page 930. In general it

may be stated from our experiences in accord with that of others that the nitrogen mustards are effective therapeutic agents in patients with various forms of lymphoma especially the generalized type of Hodgkin s disease Although it produces some benefit in patients with various varieties of chronic leukemia and in polycythemia there are other types of treatment which are superior It is contraindicated in patients with acute leukemia More recently an oral form of the nitrogen mustards Triethylene Melamine has been introduced and may be more effective in the treatment of chronic leukemia although the preparations are so new at the present time that no definite statement can be made concerning their efficacy

Urethane —In 1946 it was first reported by Paterson and her associates (*131*) that urethane (ethyl carbamate) exerted a beneficial effect in patients with myelogenous leukemia Its mode of action has been emphasized by Bastrup-Madsen (*132*) who states that it is a mitotic poison which acts on dividing cells by two main mechanisms first fewer cells enter mitosis second mitosis is arrested at the metaphase In studying tissue cultures this observer also noted that the damage inflicted on the nondividing cells is not irreparable as they are capable of continuing their growth in a normal manner when removed from contact with urethane This serves as a laboratory basis for the continuation of a maintenance dosage of the drug in patients following the satisfactory induction of a remission

Clinical experience has shown that unquestionably urethane depresses the bone marrow in patients with myelogenous leukemia Moreover if the dosage is excessive there may also be a progression in the severity of the anemia with a pronounced leukopenia and thrombopenia The preparation is valueless in acute leukemia It has been reported by Loge and Rundles (*133*) that it produces beneficial effects in multiple myeloma which is now generally regarded as a subleukemic plasma cell leukemia Our results in patients with multiple myeloma have been encouraging

In many cases of chronic myelogenous leukemia the average total daily dose necessary to induce a remission is 3 0 grams This should be given in enteric coated tablets of 0 3 each One such tablet should be given three times daily until a total daily dosage of 10 tablets or 3 0 grams is reached A beneficial effect is observed usually within three weeks as evidenced by a decrease in the total white blood cell count the hemoglobin and a relief partial or complete of the patient s symptoms Once a satisfactory remission has been induced a maintenance dose of from 1 0 to 1 5 grams should be given daily It should be kept in mind that patients receiving this drug may have an excessive depression of the bone marrow and hence the preparation should be given only to patients who are cooperative and will remain under the supervision of the physician

The patients to whom this form of therapy has been given in our experience have been troubled considerably with nausea and sometimes vomit

ing which occasionally has been distressing The drug should always be given in enteric coated tablets the medication administered during or *after meals and in some patients it may be necessary to discontinue it for* several days and resume it in smaller doses On the other hand some patients have been able to take larger doses than 3 0 grams daily over long periods without unpleasant symptoms The gastric symptoms when they occur, are present usually in the first few weeks of treatment

Patients with chronic myelogenous leukemia who are not manifesting many symptoms may be given a trial on this form of treatment or it may be employed in conjunction with roentgen ray therapy in an attempt to prolong remissions once they have been induced by the x rays

Other Measures in the Treatment of Leukemia —Folic acid antagonists ACTH and *cortisone therapy are discussed under the topic of the treat*ment of the acute leukemias (page 844) as they have their greatest use in this form of leukemia Patients with leukemia, especially the myelogenous variety have an elevated basal metabolic rate and consequently require a high caloric intake in order to maintain weight They should be urged to eat a highly nutritious diet with nourishment between meals and at night before retiring A number of years ago Friedgood (*123*) found that the administration of iodine in the form of Lugol s solution *in doses of 5 minims three times a day would* produce a temporary reduction in the basal metabolic rate and an improvement in the symptoms of patients with chronic lymphatic leukemia In my opinion however this is of little practical benefit in the management of patients with this disease

In general it can be said that the use of iron liver extract folic acid and vitamin B_{12} *is* not helpful in the treatment of any form of the malady and in any stage of the disease There are however occasionally modifying factors to this statement which should be taken into consideration Iron may be of benefit if an iron deficiency anemia co exists which it may occasionally especially in women or if there is excessive bleeding due to secondary thrombocytopenia which leads to an important loss of blood When this occurs a hypochromic anemia is found to be present in place of the normochromic variety usually *observed In the presence* of such an anemia which is not a common complication it may be anticipated that some benefit will be derived from the administration of 0 3 grams (5 grains) or 0 6 grams (10 grains) of ferrous sulfate three times daily

Ordinarily although occasionally a patient with leukemia has a macrocytic normochromic anemia there is no improvement following the administration of antipernicious anemia medication such as liver extract folic acid or vitamin B_{12} In a rare case however the intramuscular injection of liver extract *is of value Dr Frank H Bethell* of the staff of the Simpson Memorial Institute recently called my attention to a small group of five patients with leukemia whom we observed in the past 17

years who had reacted favorably to liver extract These patients had shown a reticulocyte response and a return of the red blood cell count to normal following the use of this therapeutic agent In one instance it was given orally and in the other four intramuscular injections were employed All of the patients had a monocytic type of leukemia and in one at least in whom bone marrow studies were done megaloblasts were present which suggested that liver therapy might be of benefit In some instances the red blood cell count remained normal for a period of some months In all patients however the period of improvement was followed by a recurrence of the anemia and a progression of the disease

LYMPHOSARCOMA CELL LEUKEMIA

Patients with this disease are frequently included with those suffering from lymphogenous leukemia They should be excluded from this group however mainly because it is generally believed that they have a different prognosis and reaction to roentgen ray therapy Careful exclusion of these cases will cause the length of life of patients with lymphatic leukemia to average between four and five years which is longer than is usually stated

Age and Sex —Apparently the disease more commonly affects males in our series of patients 70 per cent were of this sex The condition may appear at any age and in either sex In males however the incidence of the disorder appears to follow that of lymphoblastic leukemia in childhood and that of lymphocytic leukemia in more mature years That is it has a greater incidence in males in childhood and after the age of 60 years Among females there is no significant predilection for any age It was found in our group of patients however that between the ages of 10 and 40 years the sexes are affected equally by lymphosarcoma cell leukemia where outside of these limits there is a predominance of males with the disease It is stated by Rhoads (*134*) that "the disease is practically confined to childhood" a statement with which I am not in strict agreement

Etiology and Pathology —Lymphosarcoma cell leukemia arises when lymph tissue undergoes sarcomatous change which at first is definitely localized Eventually however the neoplastic cells emerge from the confines of the limiting tissue and appear in the circulating blood According to Rhoads (*134*) there is excellent evidence to indicate that the disease is unicentric in origin at least in some instances of lymphosarcoma In his opinion in a large proportion of patients the disease arises primarily in the lymph nodes and according to Sugarbaker and Craver (*135*) more than 60 per cent of the patients never show an extranodal lesion When such an extranodal lesion is present it is almost always in the head or neck in such sites as the tonsils or nasopharynx In the few remaining cases the condition arises primarily in the gastro-intestinal tract

Lymphosarcoma may occur anywhere in the gastro intestinal tract but *it is observed most frequently in the stomach and has its second greatest incidence in the ileum* It is reported by Libman however (*136*) that the duodenum is involved as often as the ileum an *observation that does* not appear to have been substantiated in subsequent experience

Important studies by Wiseman (*137*) and by Isaacs (*138*) furnish information for the differentiation of this cell from the lymphoblast the young lymphocyte, and the leukemic lymphocyte Of greatest assistance *in the recognition of the lymphosarcoma cell* in the circulating blood is the method of staining blood films with cresyl blue followed by Wright s stain With this technic the *lymphosarcoma cell according to Isaacs possesses* certain differential features the most marked being the peculiar characteristics of the nucleolus This is usually eccentrically placed single very rarely multiple the nucleolus stands out as a sky blue round area surrounded by a deep black rim or chromatin which is piled up around it in the true immature lymphocyte or lymphoblast under these conditions the nucleolus appears as a light blue hole or area *in the chromatin structure without the heavily staining rim* The nucleoli are more likely to be multiple in the immature lymphocytes or lymphoblasts than in the lymphosarcoma cell

The lymphosarcoma cell in films varies in size from 7 5 by 9 microns to 12 by 13 5 microns The nucleolus is usually oval or oblong occasionally being egg shaped (thicker at one end) in films Kidney shaped or notched forms are common in some specimens The stained chromatin *is coarsely reticular and somewhat spongy in structure* and the chromatin around the edge is thickened into a fairly definite nuclear wall differing in this respect from the monocyte The cytoplasm of the cell is sparse deeply basophilic and with the brilliant cresyl blue Wright s stain appears as fine blue lace work

At necropsy there is a transformation variable in extent of a great portion or all of the lymphoid tissue in the body into the lymphosarcoma *type According to Isaacs (138)* the lymphoid follicles of the small intestine and colon show this change as well as the tonsil There is pronounced involvement of the bone marrow and subperiosteal extension and in some cases the surrounding tissues All of the organs of the body show invasion with lymphosarcoma cells Among those in which this occurs are the brain the fatty envelope of *various organs* (heart kidneys aorta) the myocardium bronchi pulmonary alveolar walls thyroid esophagus thymus spleen pituitary diaphragm stomach liver gall bladder adrenals kidney ureter skin testes epididymis seminal vesicles and vas deferens The skull may show osteolytic lymphosarcomatous infiltration

It is stated by Krumbhaar (*139*) that the lymphosarcomatous lesion has some *tendency to infiltrate the splenic capsule* and perisplenic tissue

This picture is rarely found in the spleen of patients with lymphatic leukemia This observer also states that with the wide acceptance of the neoplastic nature of the leukemic process it seems reasonable to regard lymphatic leukemia and lymphosarcoma as but different expressions of neoplastic change of the cells in question

Symptoms and Physical Signs—In most instances, the earliest sign of the disease is enlargement of the cervical lymph nodes although the initial involvement may be in the superficial lymph glands in any part of the body In 40 0 per cent of our cases the first signs were enlargement of the lymph glands or spleen and in almost all instances it was the lymph adenopathy which attracted the patient s attention to the disease In 25 7 per cent of our cases the symptoms usually associated with anemia such as weakness pallor ease of fatigue dyspnea and palpitation were the ones first noticed Evidence of infection, usually of the oral cavity throat or upper respiratory passages constituted the earliest symptom in 14 3 per cent of the cases Fever was present as an initial symptom in only 1 4 per cent of our cases and hemorrhage in only 2 9 per cent

After the disease had become established the symptoms associated with the accompanying anemia were the ones most commonly experienced Following this was fever susceptibility to infection a hemorrhagic tendency pressure of enlarged lymph glands pain in the joints symptoms referable to the gastro intestinal tract manifestations of an increased basal metabolic rate and pressure of the spleen

Physical examination almost always shows evidence of a variable degree of anemia depending on the stage of the disease signs of loss of weight enlarged lymph glands most commonly in the cervical axillary and inguinal regions and sometimes a moderate enlargement of the spleen

Blood Examination—The white blood cell count may be either in the subleukemic phase with the count within the limits of normal or below normal or in the leukemic stage with an elevation of white blood cells which usually varies from 30 000 to 100 000 per cubic millimeter In our group of 70 patients classified as having lymphosarcoma 62 9 were subleukemic and 37 1 were subleukemic when first observed The percentage of cells which has previously been classified as lymphocytes usually make up 30 to 50 per cent of all cells present in the peripheral blood Careful examination will disclose however that from 10 to 30 per cent of these cells have the typical structure of lymphosarcoma cells In some cases with high leukocyte count they may comprise 98 per cent of all those present in the blood film

With a progression of the disease there is a fall in the red blood cell count and the hemoglobin percentage as a normochromic normocytic anemia develops It is usual for a moderate anemia frequently with a red blood cell count between 2 5 and 3 0 million per cubic millimeter and

a hemoglobin of 50 to 60 per cent, to be present when the patient is first observed In the advanced stages the red blood cell count may fall to less than a million per cubic millimeter The blood platelets are normal or increased in the early stages but diminished as the disease advances

Treatment and Prognosis—The duration of life in patients with lymphosarcoma cell leukemia is variable, but nearly one half of the cases succumb within one year after the onset of symptoms or the observation of a tumor The average duration of life of the entire 70 patients in our group was 31 3 months On the other hand, some patients may survive much longer For instance, one patient lived for eight, another nine, and a third for 10 years after the onset of symptoms Considerable caution should be used in treating patients with lymphosarcoma cell leukemia with the roentgen ray as they respond less satisfactorily than do those with lymphocytic leukemia In the former there is often a rapid fall in the total white blood cell count to a level where a well marked leukopenia is present and this is frequently associated with toxic symptoms such as nausea vomiting and fever Following this there is likely to be a rather sudden rise in the white blood cell count due almost entirely to an increase in cells of the lymphosarcoma type

Considerable benefit is derived from the local application of the roentgen ray for the relief of pressure manifestations In some patients moreover prolonged benefit follows roentgen ray therapy to all parts of the body which are considered to contain the major portions of lymphatic tissue In our group of patients there was no response to roentgen therapy in 17 6 per cent of the patients an unfavorable response in 23 4 per cent and responses classified as fair in 27 2 good in 12 8 very good in 8 5 and excellent in 10 6 per cent

The cause of death in the group of 70 patients studied at the Simpson Memorial Institute was considered to be toxemia in 46 9 per cent infection in 28 1 per cent debility in 9 4 per cent an unrelated cause in 9 4 per cent and hemorrhage in 6 2 per cent

Treatment of Lymphosarcoma with Nitrogen Mustard—This form of treatment is effective as it will often induce a dramatic and prompt remission in the course of the disease It is also true that it will improve the condition of the patient when no further progress can be made with roentgen ray therapy At the present time however roentgen therapy must be regarded as the treatment of choice and the use of nitrogen mustard held in reserve until the proper results are not attained with x ray The method of administering the nitrogen mustards is given on page 930

The Surgical Treatment of Lymphosarcoma—There is some evidence to support the belief that the disease has a unicentric origin that is originating as a sharply localized new growth From a theoretical standpoint, therefore it should be possible to cure the disorder surgically The difficulty arises however in determining when the disease is still in

the localized stage Some support in favor of the surgical treatment of patients with this disorder followed by roentgen therapy is provided by the studies of Gall (*140*) and Hellwig (*141*) The latter reports that of 340 patients operative treatment was performed on 130 with roentgen therapy postoperatively He observed a five year survival rate of 24 6 per cent and of 20 patients in whom it was thought that the single focus of the disease was excised 12 or more than 50 per cent remained in good health for over five years I have had no experience with the surgical treatment of this disease but with the improvement in surgical technic and after care which has reduced surgical mortality strikingly and prolonged postoperative convalescence it may be that surgery should be given consideration in those cases in which the disease appears to be localized There is however no evidence that any patient has been cured by the surgical treatment

MONOCYTIC LEUKEMIA

Within recent years it has been recognized by many hematologists that two forms of monocytic leukemia exist These may be differentiated on the basis of the predominant white blood cell in the circulating blood and the histopathologic changes that occur in the hematopoietic organs According to Downey (*142*) there is one type designated by him as the myelomonocytic (Naegeli) variety in which the monocytes are considered to develop from the myeloblasts whereas in the other form of monocytic leukemia the histiomonocytic type of Schilling these cells are derived from the reticulo endothelial system

An idea of the incidence of the two types may be gained from the following figures During the 15 year interval between 1927 and 1941 the diagnosis of leukemia was made in 495 patients at the Simpson Memorial Institute of the University of Michigan Of these 12 9 per cent were classified as the myelomonocytic variety of which 8 5 per cent were acute and 4 4 per cent were chronic Eight per cent were considered to be of the histiomonocytic variety 4 8 per cent were acute and 3 2 per cent were chronic The latter figures are in accord with those of Osgood (*143*) who estimated the incidence of histiomonocytic leukemia as varying from 3 to 9 per cent of all types of leukemia

The essential difference in the cell types between the myelomonocytic and the histiomonocytic is shown by the diagram prepared by Bethell (*49*) In general it may be said that the peripheral blood in cases of myelomonocytic leukemia (Naegeli) is characterized by the predominance of monocytes in various stages of maturity in association with a *variable number of myeloblasts and young myelocytes In histiomono*cytic leukemia (Schilling) myeloblasts are absent from the peripheral blood but occasionally a rare myelocyte may be found Monocytes which are usually fairly mature are the predominating cell *and larger histiocytes*

may be present According to Downey (142) The end products (ripe monocytes) might have an identical morphology but the intermediate and younger forms would be different'

A comprehensive general review of the subject monocytic leukemia with 204 references has been written by Evans (144)

Pathology of Myelomonocytic Leukemia —At necropsy patients with *the myelomonocytic type of leukemia are found to have* an infiltration of large mononuclear cells unassociated with hyperplasia of the reticulo endothelial system More rarely, myeloid hyperplasia is present in the various hematopoietic organs A small proportion of such cases ultimately develop the characteristic blood picture of myelogenous leukemia and changes are found in the organs which are characteristic of this disease The findings have led many investigators to regard this form of leukemia as a variant of myelogenous leukemia Naegeli (145) strongly favors this view and contends that this evidence supports the conclusion that the myeloblast is the precursor of the monocyte It is on account of the opinion held by this observer that the condition has been termed the Naegeli type of monocytic leukemia

The bone marrow is of the cellular type and is made up almost entirely of myeloblasts and mature and immature monocytes The pulp in the spleen is also cellular and the predominating cells are of the monocytic series Myelocytes may also be found in the splenic pulp but it is unusual to observe areas of myeloid metaplasia and the activity of the reticulum is not unusual Although collections of monocytic cells are found in the periportal connective tissue of the liver and also in the sinusoids, there is no increase in the number of Kupffer s cells When the lymph nodes are involved collections of monocytic cells are found in the medulla of the glands and occasionally in the cortex but there is no indication of hyperplasia of the reticulum

The Clinical Manifestations of Myelomonocytic Leukemia —There is nothing about the clinical picture of the myelomonocytic variety of leukemia which is distinctive and thereby permits one to recognize it on this basis alone

The acute type will be considered in the section on acute leukemia The chronic variety of myelomonocytic leukemia most frequently occurs between the ages of 25 and 60 years although it may be observed in infancy and old age The symptoms and physical signs resemble those seen in patients with chronic myelogenous leukemia and in previous years the patients were considered as having this form of the disease There are symptoms of anemia and evidences of fever eventually in all patients at some time during the course of the disease and these are persistently present during the latter stages of the condition In a majority of the patients there is slight enlargement of the lymph nodes Splenomegaly is observed in 90 per cent and hepatomegaly in about 60 per cent The

spleen usually shows a moderate to a gross enlargement Hemorrhagic manifestations which usually occur in the terminal stages of the condition are present in slightly less than one half of the patients Occasionally the gums are involved and sometimes there are cutaneous manifestations

Diagnosis of Chronic Myelomonocytic Leukemia —It is not possible to conclude from the history and physical examination alone that any given patient is suffering from chronic myelomonocytic leukemia In most instances the diagnosis would be that of chronic myelogenous leukemia unless the blood was examined

Blood Examination —The condition may occur in the acute subacute or chronic forms and in the subleukemic or leukemic state In most instances the total white blood cell count does not exceed 100 000 per cubic millimeter The subleukemic form of the disease is not uncommon with a count below 10 000 per cubic millimeter As the condition becomes well established the red blood cell count is usually between 2 5 to 3 0 million per cubic millimeter and the hemoglobin varies from 50 per cent (7 8 grams) to 60 per cent (9 3 grams)

The diagnosis from a hematological standpoint is based upon the type of parent cell observed in the blood and the presence of intermediate stages between it and the mature monocyte In this variety of leukemia the parent cell is regarded as the myeloblast and the relative number of these cells and the intermediate forms of mature monocytes depends upon the acuteness of the case In some instances there are relatively few young myeloid forms present but in other patients especially those with the acute varieties of the disorder the myeloid immaturity is a conspicuous feature there being only a slight predominance of monocytes Occasionally the monocytes may completely disappear and the typical picture of myelogenous leukemia develop

Treatment and Prognosis —The treatment should be with irradiation and blood transfusions as outlined in the section on the treatment of chronic leukemia The response however is somewhat less satisfactory to irradiation than it is in patients with chronic myelogenous leukemia In slightly less than one half of the patients the result produced by irradiation is satisfactory for a variable period of years In our group of patients 58 8 per cent were classified as having an unfavorable or slight if any improvement following treatment with this therapeutic agent and in 41 2 per cent the results were classified as good to excellent When compared to the effects of irradiation in patients with chronic myelogenous leukemia the results are less satisfactory for in the latter disease there was substantial improvement in 90 3 per cent of those treated The use of urethane given as directed under treatment of chronic myelogenous leukemia (page 827) is worthy of a trial

Histiomonocytic Leukemia (Schilling) —There does not appear to be a distinctive clinical picture of this condition which enables one to

differentiate it from other forms of leukemia unless the blood is carefully examined It is observed to run either an acute course which is measured in days or weeks, a subacute one of months and a chronic one of a year or more In *most* instances the interval between the time when the diagnosis is made and death occurs is short, although undoubtedly in some cases the disease had been in existence for a variable time before its true nature was recognized

In general it may be said that the acute variety of the disease resembles the acute leukemias of other types which will be discussed under that

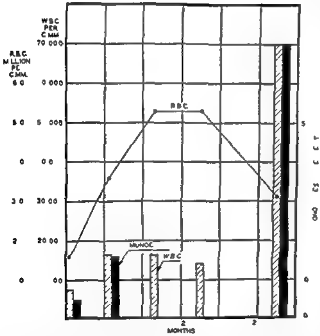


Fig 64 —The blood changes in a patient who had a macrocytic anemia with a red blood cell count of 1 6 millions per cubic millimeter When first observed the white blood cell count was 8000 per cubic millimeter and the monocytes were 4 per cent *The patient had an* achlorhydria With these findings it was thought that the diagnosis was pernicious anemia This appeared to be substantiated by the striking improvement which followed the oral administration of liver The reticulocytes however did not rise in a typical curve as is so characteristic of pernicious anemia but became leveled off at about 12 to 15 per cent *for a long period of time* With this the red blood cell count increased to normal Almost two years later the patient had a recurrence of the anemia and at this time the white blood cell count had risen to 70 000 per cubic millimeter with 70 per cent monocytes Some of the cells were monoblasts This patient then had a subleukemic monocytic leukemia which simulated pernicious anemia very closely even with the response to liver therapy which occurs in a small group of such patients with this form of leukemia

section The chronic form of histiomonocytic leukemia more closely simulates the clinical course of chronic lymphatic leukemia

Pathology —At necropsy almost all of the organs of the body are found to be infiltrated with the characteristic monocytes Especially is this true of those which contain a large proportion of the reticulo endothelial tissues such as the bone marrow the spleen and the lymph nodes There is almost always enlargement of the spleen but this may occur relatively late in the course of the disease and hence may not be apparent until a short time before death Often the lymph nodes are enlarged although

this is more likely to occur in the glands which are adjacent to areas of infection In general it may be said that the outstanding features at necropsy are evidence of hemorrhage ulceration and hyperplasia of the reticulo endothelial tissues The bone marrow is very cellular and consists largely of mature and young monocytes The reticulum is abundant and in some instances large reticular cells may be seen which are either free or loosely attached The splenic pulp is very cellular and the reticulum is hyperplastic The malpighian corpuscles are small and greatly reduced in number or they may be entirely absent Collections of leukemic cells are found in the liver both in the periportal and interlobular areas and the sinusoidal tissues Involvement of the lymphoid tissue does not occur uniformly for some parts of it show pronounced hyperplasia of the reticulum and collections of leukemic monocytes whereas in other portions there is little change

The Clinical Manifestations of Chronic Histiomonocytic Leukemia — Patients with this variety of the disease most commonly complain first of weakness or some oral or throat lesion but there are others in whom the initial complaint may be an enlarged gland dyspnea skin lesions or gastro-intestinal disturbances In most of the chronic cases the symptoms referable to an anemia are present and in about 80 per cent of the cases there is bleeding from the mucous surfaces and also petechiae of the skin at some time during the illness The lymph glands may remain normal throughout or there may be enlargement of the cervical glands only The latter result from septic lesions in the oral cavity or the throat which are so commonly present in this variety of leukemia Occasionally there is a slight generalized enlargement The spleen is palpable in about 80 per cent of the cases This is usually of moderate extent and as some say is intermediate in size between the splenomegaly of lymphatic and myelogenous leukemia The liver is frequently enlarged even in the absence of splenomegaly A patient is reported by Taylor and his associates (*146*) in whom there was renal failure with generalized edema terminating fatally At necropsy the kidneys liver and spleen were found to be infiltrated with cells characteristic of acute monocytic leukemia which accounted for the renal insufficiency The findings in the peripheral blood were typical of monocytic leukemia with a total white blood cell count of 192 000 per cubic millimeter of which 55 per cent were atypical mononuclear cells

It is usually stated that about 20 per cent of the cases have skin lesions which have been classified as exfoliative dermatitis nodules or ulcers In my experience the skin lesions have not been this common The dermatological manifestations have been collected from a study of 50 cases of undoubted Schilling type monocytic leukemia and reported by Fairburn and Burgen (*147*) They classify the lesions into six groups as follows (1) purpuric (2) maculopapular (3) plaques and nodules

(4) cutaneous suppurative conditions, (5) exfoliative dermatitis and (6) miscellaneous It is their belief that the rashes arise either by the migration of the monocytes through the capillary walls or as the result of a capillary hemorrhage They then proliferate in the perivascular regions and extend to the dermal connective tissues especially to the sheaths of the hair follicles and sweat glands They cannot exclude the possibility that in some cases the monocytes develop initially from the histiocytes found in the blood vessels sweat glands and hair adventitiae They believe that the suppurative conditions may arise as a result of impairment of local defense mechanisms by monocytic infiltrations

A subdivision into a subacute variety is a completely arbitrary one based largely on the duration of symptoms which is intermediate between the acute course and the chronic one The subacute cases resemble the acute ones in that they have the mouth lesions, and the chronic cases in that the symptoms are often mild for a considerable period of time after the disease is recognized

The Blood in Patients with Histiomonocytic Leukemia—In patients with the chronic form of the disease the white blood cell count may be below 10 000 per cubic millimeter or there may be an increase but it is not commonly above 100 000 per cubic millimeter and is usually below this level. There is always an associated anemia sooner or later in the course of the disease with a red blood cell count which varies between 2 5 and 3 5 millions per cubic millimeter and a hemoglobin percentage between 50 per cent (7 8 grams) and 70 per cent (10 9 grams)

The distinguishing feature of the circulating blood is the presence of the reticulo endothelial cells or monoblasts which differentiates this form of leukemia from the myelomonocytic type of monocytic leukemia as well as other varieties of the disease In this condition myeloblasts are absent from the peripheral blood but in some instances an occasional myelocyte is observed Monocytes which are quite mature predominate in the blood picture and their precursors the monoblasts are usually present These latter cells are characterized by the arrangement of the chromatin of the nucleus in the form of a relative coarse network the nucleoli are indistinct in the earlier forms but small and clearly outlined in the later stages The cytoplasm is blue gray and frequently contains a dense fine brick red granulation In films obtained from the bone marrow the cytoplasm of the monoblasts is usually abundant but it is often quite scanty and irregular in the cells of the peripheral blood Monoblasts differ from myeloblasts in films stained with Wright's stain as the nuclear chromatin of the former is in the form of a fine transparent network the nucleoli are inconspicuous and the cytoplasm is more plentiful and often contains fine red granules at a stage when a similar granulation is not present in the myeloblast

Treatment and Prognosis—The prognosis in cases of chronic histiomonocytic leukemia is somewhat less favorable than in patients with

Plate VI *Chronic Monocytic Leukemia*—The course of the disease in this patient was relatively rapid as death followed in seven months after the onset of symptoms No favorable effect from irradiation therapy was obtained The leukocyte count never exceeded 100 000 per cubic millimeter and anemia and thrombocytopenia were severe The two upper cells are promonocytes The lower cells from left to right are two monoblasts and a mature monocyte The chromatin of the monoblast and promonocyte nuclei exhibits a finely granular and mottle appearance In addition the blast forms possess indistinct nucleoli The cytoplasm of all cells is of the cloudy dull blue type characteristic of members of the monocyte series Azurophilic and neutrophilic granules are present in variable numbers being more abundant in the cells of greater maturity Wright's stain Magnification 960

chronic lymphatic or chronic myelogenous leukemia although the reaction to roentgen ray therapy is fairly good In our experience about two thirds of the patients have good or excellent results following this form of therapy and only one third have unfavorable reactions or do not respond at all The method of administering irradiation and the use of blood transfusions is exactly the same as in patients with other types of chronic leukemia *Arsenic* in the form of a solution of potassium arsenate (Fowler s solution) may be tried in doses beginning with 4 or 5 minims (0 25 to 0 3 cc) three times daily gradually increasing to an effective dose which may be a total daily dosage of 30 to 40 minims It should be given in fruit juices immediately following meals

The case of a patient 30 years of age with subacute monocytic leukemia is reported by Hart (*148*) as having developed a remission following the administration of aminopterin A rapid relapse occurred when the drug was withdrawn on account of the toxic manifestations which it produced resumption of therapy produced a second shorter period of improvement followed by a fatal termination A therapeutic failure in the use of the folic acid antagonists in three patients with monocytic leukemia is reported by Dameshek (*149*)

It is reported by Kinsell Rogers Baker and Jenkins (*150*) that a patient with acute or subacute monocytic leukemia age 56 responded favorably to treatment with adrenocorticotropic hormone (ACTH) in combination with blood transfusions and antibiotic therapy They observed a complete hematological and clinical remission and will provide a follow up report as to her subsequent course Urethane as given in chronic myelogenous leukemia deserves a trial (see page 827)

ACUTE LEUKEMIA

Definition —Acute leukemia is a fatal disease of brief duration most commonly encountered in childhood which is characterized by the presence of abnormal white corpuscles in the circulating blood and by an unrestrained proliferation of primitive white blood cells in the hematopoietic tissues of the bone marrow lymph nodes and the spleen Leukemic infiltrations and metaplasia or both are usually present in the organs and tissues throughout the body

Frequency and Sex Incidence —Acute leukemia occurs most frequently in childhood As shown by the statistics of Ward (*151*) its greatest incidence is in the first five years of life during which interval approximately two thirds of his cases occur Although it may develop at any time of life only 12 per cent of his cases were in persons over 50 years of age Undoubtedly in some of these cases the condition was an acute exacerbation of a chronic leukemia which had been present with few if any symptoms for a considerable period of time In our own cases of lymphoblastic leukemia 90 per cent began and terminated before the age of 20

years (A further discussion of the age and sex incidence of patients with acute leukemia will be found on page 777

For some unknown reason the acute leukemias predominate in the males, usually in the proportion of three to one It is considered by some however that in the later years of life the greater incidence of the condition in males is no longer observed

Classification —It is undoubtedly true that the general clinical picture of the various types of acute leukemias is similar, and even with a careful examination of the blood and bone marrow, there may be great difficulty in differentiating the disease into the various types Some clinicians are content to designate the condition as an acute leukemia of the stem cell type which indicates that all of the circulating white blood cells are of an exceedingly primitive variety which defy further classification Indeed the pathologist at necropsy in the past has likewise failed to accomplish much more in this direction than the clinician In more recent years however both the hematologist and the pathologist have been able in many instances, to recognize the type of acute leukemia and employ less frequently the diagnosis of stem cell leukemia In connection with this Krumbhaar and Stengel (46) state that the very difficulties of classifying acute forms which have led many to stop at the diagnosis acute leukemia have challenged us to subdivide such leukemic conditions as far as legitimate into their histogenic types in the hope of acquiring illumination of their true nature It was a pleasant surprise to find that further division of the acute types was possible in the great majority of cases Although these remarks were made with reference to the examination of material obtained at necropsy the same thought may be applied to examination of the bone marrow and the peripheral blood during life Nevertheless it must be admitted that equally experienced hematologists will differ as to the type of acute leukemia in some patients

During a period of 15 years from 1927 to 1941 inclusive we observed 495 cases of leukemia at the Simpson Memorial Institute of the University of Michigan Of these 168 cases or 33 9 per cent were designated as one of the acute varieties They were classified further into the following subdivisions

	Number of Cases	*Per Cent of Total Cases (495)*
Myeloblastic	44	8 9
Myelomonocytic	42	8 5
Lymphosarcoma	30	6 3
Lymphoblastic	28	5 4
Histiomonocytic	24	4 8
Total	168	33 9

From our observations as indicated above it is possible to state that five varieties of acute leukemia are encountered of which the myelo

blastic is the most common and the acute histiomonocytic variety is the rarest In general it must be said that in most instances the differentiation must be made from the hematological picture alone as the clinical features of all varieties resemble each other closely

Pathology —Pathologically the acute forms simulate each other very closely in their gross and microscopic appearances Despite the variety of acute leukemia which is present there is almost always hepatomegaly splenomegaly generalized lymph gland enlargement a hyperplastic bone marrow and hemorrhagic manifestations Likewise there is present in practically all cases a diffuse hyperplastic metaplasia in the bone marrow lymph nodes spleen and liver Hemorrhagic infarcts of the spleen occur in about 25 per cent of the cases Leukemic infiltrations are present in a wide variety of tissues and organs throughout the body regardless of the particular type of primitive leukemic cell involved The important difference is that in the acute forms the abnormal collection of myeloid lymphoid or monocytic cells are in the primitive blast stage whereas in the chronic the more mature forms such as the myelocytes monocytes and more fully developed lymphocytes predominate

Another constant finding is extensive and diffuse hemorrhage which involves the following organs in order of frequency skin mucous membranes especially the oral and nasal cavities and the gastro intestinal tract pericardium stomach retinae peritoneum renal tissue brain and lungs

Symptoms and Signs —The onset is usually abrupt although it is commonly preceded by some type of infection such as a tonsilitis or an ordinary cold The initial symptoms are those which are frequently seen in any severe infection namely fever malaise headache generalized aches and pains and prostration Associated with this is a rapidly developing anemia with associated pallor and commonly a tendency to bleed as indicated by purpuric spots of the skin and bleeding from mucous surfaces especially the mouth and nose There is nothing distinctive about the early clinical picture to suggest the correct diagnosis or the seriousness of the patient s condition Often the initial diagnosis is that of an upper respiratory infection or the flu until extreme prostration the pallor or tendency to bleed directs attention to the ominous nature of the illness These symptoms usually suggest a blood examination which reveals the true nature of the patient s illness for the first time

A preleukemic phase of true acute leukemia has been reported in a small group of patients by Block Jacobson and Bethard (*151A*) They state that in such a stage preceding acute leukemia usually nothing abnormal is revealed except fever evidence of abnormal bleeding and occasionally ulceration of the mucous membranes The earliest expression of marrow malfunction is a hemorrhagic tendency commonly associated with a thrombocytopenia Monocytosis neutropenia erythroblas

tosis and reticulocytosis are common Although it may be a matter of opinion as to when the true acute leukemic state develops nevertheless the authors have a good point in stating that in a certain group of patients it may be difficult to distinguish between a condition which may become leukemia and some other less ominous state They emphasize that the main problem in differential diagnosis is to differentiate the condition from toxic neutropenia aplastic anemia or hypersplenism Furthermore they emphasize that the differential diagnosis may not be clarified until the easily recognized leukemic stage develops

As the disease progresses the mouth lesions the hemorrhagic tendency the manifestations of the progressive anemia and fever dominate the clinical picture

The excessive bleeding which is associated with a secondary thrombocytic purpura, is rarely absent There is commonly bleeding from the nose, mouth, and gums and in some instances in the retinae and from the rectum and vagina It is not rare to have subarachnoid subdural or cerebral hemorrhages Eventually petechiae and ecchymoses appear on the skin In some instances, the onset of the illness is associated with the extraction of a tooth which is followed by excessive bleeding

The mouth lesions in addition to oozing of blood from the gums may be complicated by swelling ulceration and necrosis According to Forkner (*152*) in patients with acute monocytic leukemia, the patients first complaints are frequently referable to the oral cavity and hence they may consult a dentist before coming under the care of a physician This observer describes the oral lesions of acute monocytic leukemia as a diffuse swelling of the gingivae with a tendency of the teeth to become submerged in the gums There is also a diffuse cellulitis about the lesions of the mucous membranes associated with pain and signs of acute inflammation extending into the deeper layers of the tissues of the face Biopsy of the tissue of the swollen gums in patients with monocytic leukemia may show an infiltration with leukemic cells Bleeding of the gums and secondary infection often associated with Vincent s organisms may occur in any type of acute leukemia

The physical examination is characterized by a moderate to a severe pallor with evidences of bleeding into the skin and from mucous surfaces indications of a high fever and tachycardia and usually pronounced prostration The spleen is slightly or moderately enlarged in about two thirds of the acute cases It is more likely to be enlarged in the lymphatic variety but it is palpable in about one half of the cases of myeloblastic leukemia and sometimes in the monocytic varieties Never is it *grossly enlarged* in true acute leukemia In those cases with the symptoms of acute leukemia and a greatly enlarged spleen it is likely that the condition should be classified as an acute exacerbation of a chronic leukemia The liver is likely to be palpable in any type of acute leukemia But this occurs more commonly in the lymphatic than in the myeloblastic

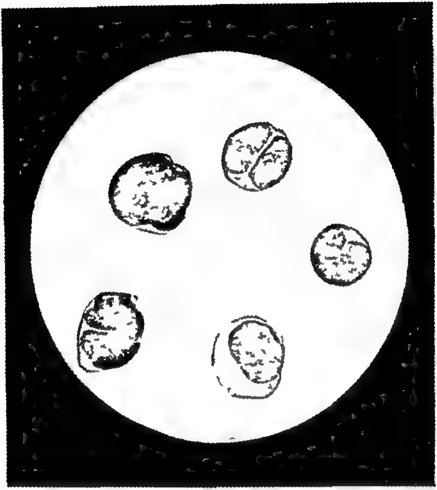


PLATE VII *Acute Lymphoblastic Leukemia* An acute process in a child of 9 years The leukocyte count varied between 50 000 and 100 000 per cubic millimeter All of the cells are lymphoblasts with the exception of the one at the lowest part of the field which is a prolymphocyte Three of the blasts show partial or complete fusion of the nucleus their chromatin is diffuse and uniformly stained nucleoli are quite distinct and cytoplasm is scanty and deeply basophilic Note the absence of platelets a finding associated with severe hemorrhagic manifestations Wright's stain Magnification 960

or monocytic forms This organ is not often greatly enlarged The lymph glands are increased in size in about two thirds of the patients but it is rare for the nodes to be so conspicuous as to have the patient notice them The cervical nodes are most commonly involved due to infection of the mouth According to Forkner (152) the lymphadenopathy is restricted to this region in patients with acute monocytic leukemia In patients with acute lymphatic leukemia there is generalized enlargement of a moderate extent and in myeloblastic leukemia it is even less conspicuous

Blood Examination —The characteristic change in the blood is the presence of a large number of mononuclear non granular cells which are either myeloblasts lymphoblasts or monoblasts Frequently at least 85 per cent of all of the cells are of a uniformly immature type and often confusion arises as to their exact identity It is often the case that few if any cells representing the intermediate stages between the mature and the primitive forms are present a fact which makes difficult the recognition of the predominant primitive cell type It becomes necessary therefore in such instances in order to recognize the variety of acute leukemia to depend upon the cytologic characteristics of the myeloblast monoblast and lymphoblast This is accomplished with difficulty in some cases even by skilled hematologists and often differences arise even among experienced observers regarding the identification of the immature white blood cells which may be present In some cases therefore it may be necessary to be content with the diagnosis of acute leukemia of undetermined type or of stem cell leukemia In recent years however there has been a gratifying decrease in the number of cases in which the type of acute leukemia could not be identified

The total number of leukocytes in the various forms of the disease is most frequently between 15 000 and 30 000 per cubic millimeter or less Rarely does the total white blood cell count rise above 100 000 per cubic millimeter From the onset there may be a count less than normal and it may fluctuate between 2000 and 3000 per cubic millimeter or less throughout the course of the disease

The *characteristic change* in the circulating blood in acute myelogenous leukemia is the presence of immature cells of the myeloid series As previously mentioned almost all of the cells in the peripheral blood may be of the myeloblast type which closely resembles both the lymphoblast and the monoblast There is a parallelism between the number of myeloblasts and the acuteness of the disease In subacute myelogenous leukemia the intermediate cell stages promyelocytes and myelocytes are present and classification can be made without difficulty

In the acute lymphatic variety some of the cells may be in the intermediate stage between the lymphoblast and the mature lymphocyte As the large cells represent the more immature lymphocyte it is this variety which predominates in acute lymphatic leukemia whereas the

small lymphocyte is the commonly encountered cell in chronic lymphatic leukemia.

In acute monocytic leukemia the predominating cells are the monoblasts and promonocytes. The monoblast has been described as having nuclei which are usually of irregular shape, frequently in the form of an irregular crescent or a broad elongated nucleus bent on itself. In some instances there is a suggestion of lobulation, although there is no distinct separation of the various lobes as seen in the polymorphonuclear neutrophils. Some of the young cells of the monocyte series have simple round, oval or slightly indented nuclei. Rarely are there nucleoli present in the nucleus of cells of the monocyte series, whereas these structures are commonly found in the nuclei of myeloblasts and lymphoblasts. The cytoplasm of promonocytes and monoblasts is usually more abundant and less basophilic than that of either lymphoblasts or myeloblasts. This is of assistance in distinguishing them from the lymphoblasts and myeloblasts in which the cytoplasm is deeply basophilic.

A severe anemia always develops, usually with considerable rapidity, in patients with acute leukemia. When the disease is well established the red blood cell count is likely to be in the vicinity of 1 million per cubic millimeter and the hemoglobin between 20 and 30 per cent. The anemia is usually of the normocytic normochromic variety, although in some instances the cell volume, as indicated by the mean corpuscular volume, may be slightly greater than normal (100 to 105 cubic microns).

Invariably in acute leukemia, as the disease progresses, there is a diminution in the number of blood platelets. In some instances they may almost entirely disappear from the blood, although usually they are present but below 50 000 per cubic millimeter. In general it may be said that a diagnosis of acute leukemia from the blood alone should be made with considerable hesitation in the presence of a normal blood platelet count.

Treatment.—Until recent years all forms of therapy in the treatment of acute leukemia were ineffective and it could not be shown that any therapeutic measure prolonged the patient's life a single day. Irradiation in the form of roentgen therapy, radioactive phosphorus (P), urethane, nitrogen mustards and arsenic are contraindicated, for when used they are usually of no benefit and in some instances are harmful.

There are two types of treatment in addition to the folic acid antagonists, ACTH and cortisone, which have been of distinct value and still are. One is the use of repeated blood transfusions. These should be given in amounts of 500 cc at daily intervals or every other day as indicated. They produce beneficial effects by combating the anemia and controlling, to some extent, in certain patients, the tendency to bleed. The other form of medication which may be of benefit is the administration of one of the sulfonamide drugs or penicillin in full doses. This

medication can be given in the form of sulfadiazine 6 grams daily in the hope that the mouth lesions with their associated pain and infection at other sites may be controlled Penicillin is even more effective in combating the infection

Folic Acid Antagonists —The basis for the use of the folic acid antagonists in the treatment of leukemia is as follows It is known that folic acid is necessary for the growth of certain bacteria and for the cells in the bone marrow In 1947 it was discovered that with relatively minor changes in the chemical structure of folic acid a group of substances known as folic acid antagonists could be synthesized These substances although biologically inert were capable of replacing folic acid in the metabolic system which governs the growth of cells The desirable effect of the folic acid antagonist however was to inhibit rather than stimulate the growth of cells This led Farber and his associates (*153*) in 1948 to employ such preparations in the treatment of children with acute leukemia The results reported by this group were startling and encouraging as about one half of the patients developed a clinical and hematological remission As prior to this time there had been no form of therapy which had the slightest beneficial result in patients with the acute form of leukemia this constituted a distinct advantage in the treatment of this disorder

A number of folic acid antagonists have been employed for this purpose all of the 4 amino type In our experience 4 amino pteroylglutamic acid (aminopterin) is a satisfactory preparation for use This compound is preferably given orally but if necessary may be given intramuscularly or intravenously in initial doses of 2 milligrams for several days and then in a maintenance dose of 1 milligram or less daily Amino an Fol is another antagonist of the same type which is satisfactory when given intramuscularly in initial doses of 20 to 41 milligrams and then in a daily maintenance dose of 10 to 20 milligrams intramuscularly

It should be emphasized that all the folic acid antagonists have toxic manifestations and that the margin of safety between the toxic and therapeutic doses is narrow The toxic effects are of two types namely destruction of the bone marrow with reduction in the number of red and white blood cells and the blood platelets in the circulating blood and a destructive action on the epithelium of the intestinal tract A sore mouth is one of the earliest symptoms of a toxic effect and is an indication for a prompt omission of the drug to continue the medication would be running the risk of causing hemorrhage from the bowel The toxic manifestations can be averted only by the careful regulation of the dosage which requires constant supervision with repeated examinations of the peripheral blood

From our own experience and that of others it may be concluded 1 in children with acute leukemia a satisfactory but temporary remis

sion may be produced in fully one half of the patients and in adults this occurs in about 30 per cent of the patients 2 This remission may persist for several months Our longest one is now of 10 months duration and the patient is still in this state 3 The therapy is valueless in patients with chronic leukemia

It is our belief that the prospect of producing satisfactory results in acute leukemia with antagonist therapy is best in patients in whom the blood and bone marrow are typical of acute leukemia but the condition is not fulminating and without extensive bleeding The outlook also appears to be better in the subleukemic state in young persons and in the lymphocytic rather than the acute granulocytic or monocytic types It has been our policy to continue the therapy in a maintenance dosage after a remission has been produced

In many patients the remission persists for five or six months and then a refractory stage develops The cause of the eventual failure of antagonist therapy has been investigated by Burchenal and his associates (154) They found a strain of leukemic cells in mice that was initially sensitive to folic acid antagonists which eventually developed a resistance to this preparation The cause for this was not apparent there was no anatomical changes observed which might explain it If the mechanism of this resistance could be determined and overcome then a real contribution to the treatment of leukemia could be made

ACTH and Cortisone —The possibility that cortisone and ACTH might be of value in the treatment of leukemia is based on the observation of Dougherty and White (155) that there is a decrease in the lymphoid tissue in animals following the injection of adrenal cortical substance Furthermore these same authors demonstrated that following the injection of adrenocorticotropic hormone into mice there was an extreme lymphopenia (156) In addition Heilman and Kendall (157) in 1944 demonstrated that injections of compound E prevented the transplantation of a rapidly growing lymphosarcoma in susceptible mice and once the growth had been established it caused retrogressive changes temporarily

These observations have led to a trial of both ACTH and cortisone in a limited number of patients with either acute or chronic leukemia of the myelogenous lymphatic and monocytic types as well as in multiple myeloma Our experience is too incomplete at present to express a definitive conclusion regarding the action of these two preparations in patients with leukemia It is only possible to say that they have a temporary salutary effect in certain patients with the disease Many more studies on patients with different types of the disorder should be obtained before an opinion can be expressed

In the meantime it may be said the following tentative conclusions may be ventured with the understanding that they may be radically revised with additional experience 1 At least two thirds of the children with

acute leukemia may show clinical evidence of improvement and about one third may have a definite hematological remission which in some cases may be complete and in others partial 2 The best results are observed in children with acute lymphatic leukemia much poorer results are seen in acute myelogenous and monocytic leukemia and in some it is not conceded that the medication is of any benefit 3 When remissions are produced they are temporary usually persisting from only four to eight weeks but some have continued as long as 30 weeks when relapse occurs a second remission may or may not follow, although as many as four remissions have been observed in a single patient 4 Symptoms such as those associated with Cushing s syndrome are commonly observed being reported in as many as 85 per cent of some groups who have received this treatment 5 The results produced in patients with acute leukemia with ACTH or cortisone are inferior to those seen following the use of the folic acid antagonists judging from the effect on the blood and the bone marrow 6 In patients with acute leukemia it is possible to induce a further remission with ACTH or cortisone after they have become refractory to folic acid antagonist therapy 7 The dose which has usually been employed has been 50 milligrams of ACTH a day for infants and 100 milligrams a day for adults Cortisone has usually been given in doses of 150 milligrams daily for infants and 300 milligrams daily for adults for limited periods

It is of interest to note therefore that these preparations are capable of reversing a leukemic condition even if only for a brief period Furthermore the possibilities that a combination of folic acid antagonist and cortisone or ACTH therapy may be of greater value in the treatment of acute leukemia than one of the preparations alone should be given consideration

A new drug 6 Mercaptopurine an analogue of the nucleic acid constituent adenine and the physiologic purine base hypoxanthine has recently been introduced as a form of therapy in patients with acute leukemia It was first synthesized by Hitchings and his associates (*157A*) and found to produce regressions in sarcoma of mice by Clarke *et al* (*157B*) and first given a clinical trial by Burchenal and his associates (*157C*) It is thought to act as an antipurine instead of an antifolic acid agent and it will be of importance to note if beneficial effects are produced in patients with acute leukemia who have become refractory to the antifolic acid preparations At present it should be given only to patients in whom antifolic acid preparations and steroids are ineffective and in those in whom daily blood counts can be done as a control to the therapy. The initial dose advised is 2 5 milligrams per kilo orally per day. At the first sign of fall in the leukocyte count the drug should be discontinued for several days and then cautiously resumed

Prognosis —The disease usually has a fulminating course and terminates fatally within a few weeks to a few months In speaking of acute

lymphatic leukemia Bethell (158) correctly terms it as a cataclysmic disaster of childhood This is not only true of the lymphatic variety of acute leukemia but also of the others although as Bethell recognizes acute leukemia is not limited to young patients

In the past the disease almost without exception has run a brief course as shown by the fact that more than three fourths of the patients succumb within 8 weeks after the appearance of the initial symptoms and more than one fifth die after a brief illness of two to three weeks Occasionally the disorder will change from an acute to the subacute or chronic phase but this is rare and even then the duration of life is ordinarily not greater than six months

Since 1948 with the introduction of the folic acid antagonists and ACTH and cortisone these new agents have at least shown that the acute process is reversible if only for brief intervals and hence a gleam of hope can be held out for the further development of new and improved methods of therapy which may be developed in the not too distant future The effects of these therapeutic agents is discussed under the appropriate headings on page 846 and page 878 and hence need not be repeated here

SUBLEUKEMIC LEUKEMIA

In the past there has been some confusion in regard to this condition largely due to the many names which have been given it It has been referred to as pseudo leukemia aleukemic myelosis aleukemic lymphadenosis aleukemic leukemia aleukemic erythroblastosis and many others Present day usage however accepts in general the definition of the following terms A patient with leukemia is said to have *subleukemic leukemia* when the leukocyte count does not exceed 15 000 per cubic millimeter and it often is below this yet with the type cells present in sufficient numbers in the circulating blood to indicate the diagnosis *Aleukemic leukemia* is considered to be present when the leukocyte count is below 15 000 per cubic millimeter and yet the type cells in the circulating blood are absent or so few that the diagnosis cannot be made by examination of the blood alone In general it seems permissible to use the term subleukemic in most instances as a general term to include both the subleukemic and aleukemic varieties as defined

It is recognized that there may be a stage of either the chronic subacute or acute myelogenous lymphatic monocytic lymphosarcoma cell leukemia or plasmocytic leukemia in which the white blood cell count is either normal or below normal Subleukemic leukemia is therefore a form of the disease in which all the usual features of the condition are present with the exception that the number of the white blood cells in the circulating blood is not increased above normal In some instances they are decreased to the level of a pronounced leukopenia and in others there may be so few abnormal circulating white blood cells that the diag

nosis of leukemia is difficult from the blood alone or in case of the aleukemic types there may be no recognizable abnormal white blood cells in the blood stream Subleukemic leukemia may 1 persist throughout the course of the patient s illness 2 it may begin with the subleukemic and terminate with the leukemic phase or the reverse of the situation may occur and 3 it may change from one form to the other one or more times spontaneously or as the result of therapy

Frequency of the Subleukemic Phase —Reliable figures dealing with the frequency of subleukemic leukemia in relation to all forms of the disease are not available Recently Bethell (*158*) has compiled figures giving the incidence of subleukemic lymphatic leukemia in a group of patients with the acute and chronic types of the disease He found that in 434 patients with all forms of leukemia observed at the Simpson Memorial Institute between the years 1928 and 1940 that 190 or approximately 44 per cent had lymphatic leukemia and that also 44 per cent of these were subleukemic in accordance with his definition of this state as defined by him when first observed This information would indicate that almost one half of the patients with lymphogenous leukemia are in this phase of the disease when first examined at the Institute A further analysis shows that the subleukemic phase is present in 53 8 per cent of patients with lymphoblastic (acute) leukemia in 52 9 per cent of patients with lymphosarcoma cell leukemia and in 11 per cent of patients with chronic lymphocytic leukemia Leukopenia or a leukocyte count within normal range is observed least often in the myelocytic variety which is the commonest form of leukemia

The Importance of Recognizing the Subleukemic State —The recognition of the subleukemic state is of importance chiefly for two reasons First patients who have chronic leukemia and a white blood cell count below 15 000 may be denied the improvement which is offered by the use of roentgen therapy or the use of radioactive phosphorus (P^{3}) Its presence does not necessarily contraindicate the use of nitrogen mustard or folic acid antagonists or urethane but it does indicate that caution should be used in the application of these drugs as a severe and undesirable leukopenia may result The second reason is that when subleukemic leukemia exists in a patient the condition is often not recognized as such The acute form may be incorrectly regarded as thrombocytopenic purpura and the chronic form as Banti s disease aplastic anemia Hodgkin s disease myelophthisic anemia or pernicious anemia Moreover the diagnosis of subleukemic myelogenous leukemia is not infrequently made in patients with leukemoid reactions such as those seen in neoplastic invasion of the bone marrow or miliary tuberculosis or the myeloid metaplasias as described by Jackson and his associates (*159*)

Diagnosis —The condition is characterized by the following 1 In all cases in which the diagnosis of subleukemic leukemia is made of

course the arbitrary definition implies there are a sufficient number of pathologic cells such as myeloblasts, myelocytes, lymphoblasts mono blasts, lymphosarcoma cells or plasmoblasts in the circulating blood to make the diagnosis There is no question but what in occasional patients with leukemia there is a true aleukemic state in which the white blood cell count is below 15 000 and there are an insufficient number of abnormal white blood cells in the circulating blood to recognize that the patient has leukemia To a certain extent, the recognition of these cells requires an expert opinion in some cases and it also depends on how frequently and how extensively the blood has been examined *In almost all instances*

TABLE XXXVIII

SUBLEUKEMIC LEUKEMIA MAY HAVE ANY ONE OR MORE OF THE FOLLOWING AS THE PRESENTING FEATURE OF THE DISEASE

1 Severe Normocytic or Macrocytic Normochromic Anemia	5 Tumefaction of the Gums
2 Lymphadenopathy	6 Pronounced Leukopenia
3 Splenomegaly	7 Bizarre Cutaneous Lesions
4 Fever	8 Changes in Bone

TABLE XXXVIII—*The recognition of subleukemic leukemia may present one of the most difficult problems in the differential diagnosis of blood diseases The condition is not in frequently regarded as Banti's disease aplastic anemia Hodgkin's disease myelophthisic anemia or pernicious anemia It is especially difficult in some cases even with the information derived from sternal puncture to be sure whether the patient has subleukemic leukemia or aplastic anemia In patients referred to us with the statement that they have pernicious anemia which is resistant to all forms of antipernicious anemia therapy it is not unusual to discover that they are suffering from subleukemic leukemia instead of the former disease Most commonly the main feature of the condition is either a pronounced normocytic or slightly macrocytic anemia a few isolated enlarged lymph glands or a palpable spleen In most instances the correct diagnosis of subleukemic leukemia can be made by means of a sternal puncture and study of the marrow thus obtained by an experienced observer*

however of either subleukemic or aleukemic leukemia the differential formula is abnormal 2, A progressive normocytic, normochromic anemia often of a severe grade which is with exceedingly rare exceptions mentioned later, refractory to all forms of therapy 3 The demonstration by sternal aspiration of myeloblasts lymphoblasts monoblasts lymphosarcoma cells or plasmoblasts in sufficient number in the marrow to indicate that the patient has leukemia 4 Commonly a thrombocytopenia This reduction of platelets is prone to develop in the acute exacerbations of the disease and as a terminal event When present it is almost always accompanied by bleeding into the subcutaneous tissues and from the mucous membranes and usually is regarded as an ominous prognostic sign

The diagnosis of a condition should always be considered in the presence of any one of the following 1 leukopenia with or without a normocytic or macrocytic anemia 2 unexplained lymphadenopathy or splenomegaly, 3 fever without obvious cause 4, tumefaction of the

gums 5 a hemorrhagic tendency 6 certain characteristic cutaneous lesions and 7 pain in the bones and about the joints and tenderness of the sternum

Treatment and Prognosis —In my experience it has not been possible to apply roentgen ray therapy effectively in such patients because the already diminished white blood cell count falls to such a low level as a result of these treatments that further exposures are contraindicated Usually it has done more harm than good Such patients should be given repeated blood transfusions and also treated for any associated infection with antibiotic therapy It is permissible to try the cautious use of urethane in patients with chronic subleukemic myelogenous leukemia if they are kept under close observation This drug may cause an increase of leukopenia which is undesirable In acute leukemia and an associated leukopenia the use of folic acid antagonists is permissible also *provided the treatment is controlled with daily blood examinations* In a few instances patients with chronic subleukemic or aleukemic leukemia experience a spontaneous increase in the white blood cell count to the point where roentgen therapy may be employed This has not been a frequent occurrence in my experience

Occasionally patients with subleukemic monocytic leukemia have a macrocytic anemia with a megaloblastic marrow When this condition is present it is permissible to use liver extract 1 cc (15 units) intermuscularly daily for one week and then three times weekly as a trial This may control the anemia temporarily

EOSINOPHILIC LEUKEMIA

It is not uncommon to observe an increase in the percentage of eosinophils in the circulating blood in patients with myelogenous leukemia In a few cases however it has been observed that the eosinophils outnumbered all other types of white corpuscles For example the total white blood cell count has been reported as numbering from 100 000 to 200 000 per cubic millimeter and the percentage of eosinophils have comprised from 50 to 90 per cent of all of the white blood cells in the peripheral blood In such patients however the eosinophils are chiefly of the mature types some even having hypersegmentation of the nucleus although there have usually been from 2 to 5 per cent which have been classified as eosinophilic myelocytes

This condition most frequently occurs in males between the ages of six and 54 years although cases have been reported in females There has always been an associated enlargement of the spleen the course has been that of a myelogenous leukemia with an eventual fatal termination and at death the organs have shown a leukemic infiltration

Some observers have considered the disorder as differing from leukemia chiefly because the cells in the circulating blood have been largely of the

mature, rather than the immature types Otherwise the increase in the leukocytes the splenomegaly, the fatal course and the leukemic infiltration found at necropsy all indicate to me that the condition is merely a variant of chronic myelogenous leukemia and should be treated as such Recently Evans and Nesbit (*160*) and Gray and Shaw (*161*) have reviewed the literature with reference to this disease

Prognosis and Treatment —There is nothing to indicate that the course of the disease in a patient with eosinophilic leukemia is in any way different from that of any type of myelogenous leukemia Cases of the acute and chronic types and of the subleukemic variety have been reported Care should be taken to eliminate other conditions which may be associated with an increase in eosinophils such as parasitic infestations especially trichinosis allergic states and malignant disease

It has been pointed out by Blackburn (*162*) that Hodgkin s disease periarteritis nodosa trichinosis as well as less clearly understood febrile diseases can produce a pronounced eosinophilia which suggests the possibility of leukemia In a patient reported by him there was a leukocyte count varying between 60 000 and 100 000 per cubic millimeter with the eosinophil percentage ranging from 64 to 90 per cent Material compatible with the diagnosis of eosinophilic leukemia was aspirated from the bone marrow At necropsy the patient exhibited all of the characteristic changes of periarteritis nodosa

BASOPHILIC LEUKEMIA

An increase in the basophils of the circulating blood always suggests the possibility that the patient may be suffering from leukemia as there is no condition in which this occurs more regularly It is probable that cases of the so called basophilic leukemia are those in which myelogenous leukemia is present and there has been merely an exaggeration of the tendency toward basophilia which is frequently observed in this disorder The condition is not common In a 10 year period in which 300 cases of leukemia were seen Doan and Reinhart (*163*) observed only five cases which they classified as myelogenous leukemia of the basophilic type

In some patients the basophils in the circulating blood may reach 50 per cent or more with a leukocyte count which is from 100 000 to 200 000 per cubic millimeter There may also be numerous immature basophils in the circulating blood as well as mature forms and an increase in the number of neutrophils In a patient I saw recently the white blood cell count had been as high as 30 000 per cubic millimeter and the basophils 19 per cent This patient s disease had been discovered as an incidental condition by the routine examination of blood

Apparently the disorder does not differ importantly from the acute and chronic forms of myelogenous leukemia and hence the treatment and prognosis is the same as in that variety of the malady

It is known that megakaryocytes may occur in the circulating blood in various conditions although they are usually undetected unless the studies are made by an experienced observer. Minot (*164*) reported that these cells may be found in the blood of patients with myelogenous leukemia, polycythemia rubra vera, Hodgkin's disease, and in some cases with infection. This author pointed out they might appear in relatively large numbers in the blood of patients with myelogenous leukemia. Furthermore it is known that they may be found in the tissues, particularly in the spleen, liver, lymph nodes, lungs, and kidneys of patients with both the subleukemic and leukemic types of myelogenous leukemia. According to Minot (*164*) these cells were observed in 35 of 45 cases of chronic myelogenous leukemia and in some instances they may make up an appreciable number of all nucleated cells present in the circulating blood.

It does not seem correct to regard such cases as a separate type of leukemia as they do not vary clinically from myelogenous leukemia except for the presence of megakaryocytes in the circulating blood and in the various organs. Likewise the condition known as "aleukemic megakaryocytic myelosis" is probably not a true leukemia, for as Downey has emphasized, in this condition there is a diversity of cell types in metaplastic organs and the bone marrow, and furthermore there is an absence of the characteristic leukemic infiltrations. It is suggested by Downey (*165*) that it be designated by the name "myeloid megakaryocytic hepatosplenomegaly." Carpenter and Flory (*166*) likewise agree that it is a nonleukemic condition and suggest the name of "chronic non-leukemic myelosis."

Recently Whitby (*167*) has reviewed the significance of megakaryocytes in the circulating blood and emphasized that when such cells appear the diagnosis of myelofibrosis with extramedullary blood formation should always be considered.

LEUKEMOID REACTIONS

It is now appreciated that there are a considerable number of conditions in addition to true leukemia in which immature white blood cells may appear in the circulating blood in association with a normal, increased, or decreased leukocyte count. In every patient in whom the diagnosis of leukemia is considered, therefore, these conditions should be kept in mind, for if any of these states are present instead of leukemia the treatment and prognosis is, of course, altered importantly. Such blood pictures simulating the alterations in the blood of leukemia are called leukemoid reactions. The highly important differentiation between such conditions and leukemia can usually be accomplished by continued clinical observation, repeated blood examinations, and a study of the sternal bone marrow.

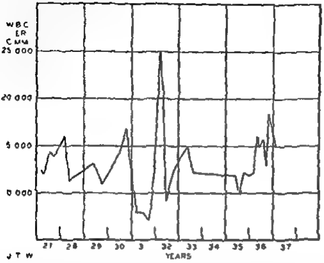


Fig 65 —Leukocytosis (in a physician age 54 when first seen) had existed for a period of at least 10 years Most of this time his complaints were of weakness ease of fatigue and vague abdominal discomfort Almost every type of examination including removal of a normal gall bladder were done and no cause for the continued leukocytosis was found The patient died away from the hospital and his exact subsequent history is not known Two other patients with a similar leukocytosis have been observed One a robust, active healthy business executive has had a persistently elevated white blood cell count for several months for which no obvious explanation could be found The other a 38 year old physician has had an elevated white blood cell count for about two years without an obvious explanation When last seen the leukocyte count was 25 000 per cubic millimeter and he complained of ease of fatigue which compelled him to work about one half of the time The question arises as to whether such patients have an early leukemia or some obscure infection as a basis for their increased white blood cell count I am inclined to favor the latter view although in a patient with an elevated white blood cell count for which no cause can be found the suspicion must arise that the patient has an early stage of leukemia

Leukemoid reactions have been divided into two types by Krumbhaar (*168*) as follows 1 those that present a real difficulty in diagnosis from leukemia, and 2 those that have a hematological similarity only He mentions the following diseases as having blood pictures which may simulate leukemia closely infectious mononucleosis miliary tuberculosis measles and pertussis acute infection with lymphocytosis acute infection with hemorrhage terminal septicemia bone marrow intoxication (mustard gas poisoning) with a terminal picture like that of acute myeloid leukemia agranulocytosis offering some diagnostic resemblance to acute leukopenic leukemia myeloma which may be differentiated from acute leukemia at the autopsy table only cases with a terminal leukemia blood picture and acute gastrocolitis and Banti s disease respectively It is pointed out by Krumbhaar that of the 10 cases reported by him although the blood pictures were indistinguishable from one of the various forms of leukemia in only three however was the clinical diagnosis difficult

A patient with monocytic leukemia associated with active tuberculosis of the spleen has been reported by Heller and Hiles (*169*) The question arose as to whether the patient had two separate conditions coincidentally associated or whether the blood changes were a leukemoid reaction to

an active tuberculous infection. Necropsy indicated that the association of the two diseases was probably fortuitous.

Leukemoid reactions of the myeloid type have been studied by Heck and Hall (*170*) who report such changes in the blood as occurring in the following conditions: acute infections or acute exacerbations of chronic disease; in various hemolytic anemias such as "crises" of congenital hemolytic anemias due to poisoning by chemical substances and in the rare cases of hemolytic anemia of unknown cause; in pernicious anemia; in polycythemia vera; in Hodgkin's disease and associated diseases; in essential thrombocytopenia; in erythroblastic anemia; following the acute loss of blood; in granulocytopenia; in different types of severe anemia due either to cases with increased regenerative activity of the bone marrow after acute loss of blood or in the hemolytic anemias; in metastasis of a malignant process to bone; in multiple myeloma; in osteosclerosis; in diabetic coma; in chemical poisoning; and occasionally in some patients in whom a satisfactory explanation cannot be found at necropsy.

A leukemoid condition has been arbitrarily defined by Hill and Duncan (*171*) as follows: It is considered to be a reaction simulating the blood picture of leukemia in which the following are found: (1) a total leukocyte count over 50,000 per cubic millimeter; (2) presence of immature cells of the "blast" stage; or a combination of both (a) and (b). They offer the following classification of leukemoid reactions of the myeloid type according to the apparent causative mechanism.

CLASSIFICATION OF LEUKEMOID REACTIONS OF MYELOID TYPE ACCORDING TO APPARENT CAUSATIVE MECHANISM

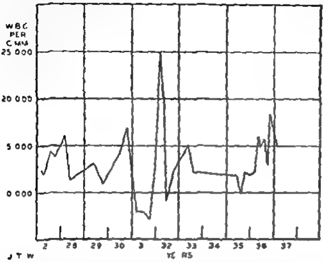
I. Bone Marrow Irritation or Stimulation. This may be physical, chemical, or allergic in character.

A. General Features of Blood Picture

1. High leukocyte count, often over 75,000.
2. Eosinophilia and basophilia frequently prominent.
3. Degree of leukocyte immaturity less marked than in II and III; usual myelocytes with few or no myeloblasts.

B. Conditions or Diseases Capable of Producing This Type of Reaction

1. Osteomyelitis and complicated bone fractures.
2. Metastatic carcinoma of bones.
3. Chronic infectious granulomata of bone.
4. Hodgkin's disease with bone marrow lesions.
5. Severe reactions to intravenous medication.
6. Severe reactions following transfusions.
7. Pyogenic infections.



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leukemia are helpful in differentiating it from a leukemoid reaction 1 60 to 70 per cent or more of the circulating white blood cells are of a uniformly large immature "blast" type 2 a normocytic or slightly macrocytic anemia often of a severe grade usually develops during the course of the disease and 3 the blood platelets are almost always reduced in number

Lymphatic leukemoid reactions are observed in a number of diseases including pertussis typhoid fever and infectious mononucleosis. The latter condition which is characterized by complaints referable to the upper respiratory passages and fever lymphadenopathy a palpable spleen in 50 per cent of the cases and atypical lymphocytes in the circulating blood should receive most careful consideration in all young persons in whom the diagnosis of leukemia is a possibility Of considerable assistance in the differential diagnosis is the heterophile antibody reaction which is usually positive in infectious mononucleosis and almost without exception negative in leukemia Recently however two patients with monocytic leukemia have been reported as having a positive heterophile antibody reaction in relatively high titer (see page 968)

It is emphasized by Smith (*172*) that a condition which he designates as acute or chronic infectious lymphocytosis may occur in young children and that this may be confused with either infectious mononucleosis or lymphatic leukemia This condition is however differentiated clinically hematologically and serologically from infectious mononucleosis leukemia and infections which are commonly associated with lymphocytosis The sheep cell agglutination test is negative in both the acute and chronic types of the syndrome and the bone marrow shows only an increase in the number of lymphocytes In the acute type of infectious lymphocytosis there is a transient unexpected hyperleukocytosis with an absolute and relative increase in the lymphocytes which is associated with recognizable symptoms and physical signs characteristic of an upper respiratory infection In the chronic type there is a low grade fever often present for weeks or months and symptoms such as anorexia pallor fatigability and para umbilical pain In both conditions the total white blood cell count may reach 50 000 to 75 000 per cubic millimeter or more and the proportion of lymphocytes be 80 to 90 per cent The course of either type of the disease is benign there is no lymphadenopathy splenomegaly or clinical manifestations which are characteristic of infectious mononucleosis or leukemia These differences and the results of the sternal puncture together with the absence of abnormal lymphocytes in the blood should readily differentiate the condition from either infectious mononucleosis or leukemia

Extramedullary Hematopoiesis—This subject has been discussed briefly on page 855 in relation to leukemoid reactions but additional reference is made here for the sake of completeness In infancy the red

II LIBERATION LEUKOCYTOSIS Marrow response to overwhelming demand

A General Features of Blood Picture

1 Leukocyte count variable usually less than in Group I
2 No definite eosinophilia in most cases
3 Degree of leukocyte immaturity generally greater than Group I

B Conditions or Diseases Capable of Producing This Type of Reaction

1 Acute hemolysis in
  (a) Sulfanilamide therapy (and related drugs)
  (b) Familial hemolytic anemia
  (c) Blackwater fever of malaria
  (d) Sickle cell anemia
  (e) Hemolytic poisons phenylhydrazine and so forth
2 Erythroblastic anemia
3 Pernicious anemia in crisis
4 Following severe hemorrhage
5 Recovery phase of granulocytopenia
6 Polycythemia especially in anemic phase such as following therapy
7 Septicemia
8 Stage of impending death in acute infections

III Ectopic Hematopoiesis Formation of blood producing foci outside of bones usually due to destruction or crowding of bone marrow

A General Features of Blood Picture

1 Leukocyte count relatively lower, often in normal range
2 Eosinophilia not prominent
3 Degree of leukocyte immaturity more marked than in Groups and II

B Conditions or Diseases Capable of Producing This Type of Reaction

1 Osteosclerosis and osteofibrosis
2 Prolonged increased demand in
  a Chronic form of familial hemolytic anemia
  b Prolonged untreated pernicious anemia
3 Tumors with extensive replacement of bone marrow
4 *Lipoid histiocytosis*

As hematopoietic tissues in infancy and childhood are more likely to react abnormally to various stimuli especially infections extreme caution should be used before concluding that the changes in the blood of a young person are of a leukemic nature Confusion is more likely to arise with the alterations observed in the acute leukemias In this condition three important and almost constantly occurring changes in acute

define myelofibrosis as fibrosis of the bone marrow which must be considered separately from osteosclerosis as this means an excessive proliferation of endosteal bone. A complete classification is given which divides myelofibrosis into two main types namely 1 focal and 2 secondary. Each of these are divided into the primary and secondary types. The paper by these authors is concerned primarily with generalized myelosclerosis and particularly with the primary or idiopathic type. They consider that the etiology of this condition is unknown but such factors as occlusion of blood vessels and hormones must be given consideration. It is pointed out appropriately that myelofibrosis is not similar to aplastic anemia. The marrow is fibrotic in the former and may be fatty in the latter; furthermore extramedullary hematopoiesis is present in the former but not in the latter.

Osteosclerosis with Changes in the Peripheral Blood Simulating Leukemia.—It has been recognized that a generalized osteosclerosis which involves the bone marrow with extensive osseous hyperplasia and associated fibrosis of the medullary stroma may occur with the resultant disappearance of the hematopoietic parenchyma and changes simulating leukemia in the circulating blood. In an effort to compensate for the replacement of the hematopoietic tissue in the bone marrow there is extramedullary formation of blood cells which has been observed in the spleen, liver and the lymph nodes. Depending upon the nature of the alterations of the cells of the circulating blood and other clinical findings these cases have been described as examples of osteosclerosis with myeloid leukemia, subleukemic myeloid leukemia, lymphatic leukemia, anemias of various types and polycythemia.

The condition is observed in adults and there is no indication that there is a familial incidence. The findings on physical examination are evidences of an anemia of variable degree and an enlargement of the spleen, liver and lymph glands. In a very great majority of the reported cases there have been immature erythrocytes and granulocytes in the circulating blood. Although there has been some confusion in the interpretation of the blood changes, in general it may be said that those patients with immature forms of granulocytes and an increased white blood cell count have erroneously been regarded as having chronic myelogenous leukemia and those with immature granulocytes and a normal or reduced white blood cell count have been considered to have a subleukemic form of the same disease.

Confusion in the diagnosis of chronic myeloid leukemia with osteosclerosis is illustrated by the following case. A 55 year old male reported by Jordan and Scott (*175*) who give a full review of the literature had a white blood cell count between approximately 22 000 and 32 000 per cubic millimeter and the granulocytes made up over 85 per cent of all of the white blood cells with 19 per cent of them being myelocytes. The

blood cells the granulocytes and the platelets are formed in the spleen liver, thymus bone marrow and other organs At about the eighth month of intrauterine life only the bone marrow functions in this capacity In infants *blood forming marrow is widely distributed* throughout the skeleton but in adult life it is limited to the ribs the vertebrae scapulae pelvic bones and small areas in the upper end of the femur and the humerus

Although the extramedullary areas of bone formation are inactive in adult life nevertheless they are a potential source of red blood cells granulocytes and *platelets as they can become reactivated when the* bone marrow fails for one reason or another in its important function Apparently the rests or cells that remain from intrauterine life, are the potential *sources of erythrocytes granulocytes and platelets* They remain quiescent but ready to supply the cells which they are capable of producing when the need is present

The presence of a secondary or compensatory extramedullary hemopoiesis is usually indicative of a serious and widespread blood disorder As emphasized by Rosenthal (*173*) the presence of extramedullary blood formation is suggested by three findings 1 When the blood picture is one of leukoerythroblastosis as indicated by the presence of both erythroid and myeloid immature elements in the circulating blood In some instances the number of immature white blood cells is so numerous that the diagnosis of leukemia is at once suggested In others the nucleated red blood cells predominate and the diagnosis of a hemolytic anemia must be considered And finally there may be a great increase in the number of blood platelets bizarre giant platelets or megakaryocytes in the circulation The latter may be in such numbers as to suggest the possibility of a megakaryocytic leukemia about which there is a dispute as to whether it is a clinical entity 2 The presence of enlarged organs known to participate in extramedullary blood formation such as the spleen liver and lymph nodes 3 The demonstration by aspiration or biopsy that these organs are participating in extramedullary blood formation

Extramedullary blood formation may occur in association with a wide variety of conditions which may be divided into three types as suggested by Rosenthal namely 1 that due to relative bone marrow failure as in chronic blood loss hemolytic anemia pernicious anemia hypersplenism 2 those associated with destruction *of the normal bone marrow* elements due to septicemia chemical exposure or radiation and 3, those secondary to replacement of normal marrow as in carcinomatosis Hodgkin s *disease of bone* multiple myeloma osteosclerosis myelosclerosis lipoidosis and Paget s disease

A comprehensive clinical and pathological study of *primary and secondary myelofibrosis* is contributed by Erf and Herbut (*174*) The authors

in the bone marrow as an intrinsic part of the proliferative marrow disorder

Clinical Findings.—The condition is characterized by weakness, abdominal distress, a hemorrhagic tendency, and a slowly progressive splenic enlargement due to myeloid metaplasia. The blood picture is almost identical with chronic myelogenous leukemia, but it may also resemble chronic hemolytic anemia. There may be a slight depression or elevation of the white blood cell count. Immature white blood cells and red blood cells are characteristically present in the blood stream.

The diagnosis of myeloid metaplasia can only be made during life by the finding of myeloid cells in the material obtained by splenic puncture with histologic evidence that the bone marrow has not undergone leukemic changes. When this combination of findings is present in a patient with the characteristic blood picture of chronic myelogenous leukemia, the diagnosis is suggested. *One should suspect the correctness of the diagnosis of myelogenous leukemia when the sternal puncture fails to reveal the presence of leukemic changes.* From a clinical standpoint the condition may be confused with myelogenous leukemia. According to Reich and Rumsey (*177*), who report 5 cases, the pathologic diagnosis at necropsy is likely to be confused with atypical Hodgkin's disease or atypical leukemia. From the observations previously cited that some of these cases follow the exposure to industrial solvents, a careful inquiry should be made of all patients suspected of having the disease concerning contact with benzol, paint remover, carbon tetrachloride, and other similar chemicals.

Prognosis and Course.—A great majority consider that irradiation and splenectomy are of no benefit and may be harmful. If one is uncertain of the diagnosis, then a period of careful observation should be carried out at which time only blood transfusions and symptomatic treatment should be given. The duration of life from the onset of symptoms to the date of death was almost 11 years in Jackson's cases (*159*). On the other hand, one patient, a Negro, age 48 years, who was observed by Reich and Rumsey (*177*) succumbed within five months after the onset of the initial symptoms.

The opinion that splenectomy is contraindicated is by no means unanimous. A report of the results of splenectomy in five cases of agnogenic myeloid metaplasia of the spleen has recently been made by Green, Conley, Ashburn, and Peters (*177A*). Four of the five patients had been under observation for more than four years since the spleen had been removed. When these patients are considered along with a review of a group of cases in the literature, they conclude that the information thus obtained fails to confirm the belief concerning the harmful effects of splenectomy due to removal of a large blood forming area. They do state, however, that the operative risk is considerable and most patients

cervical and axillary lymph nodes were slightly enlarged the liver edge extended 7 to 8 cubic millimeters below the right costal margin, and the spleen to the level of the iliac crest The patient survived for a period of two years but eventually succumbed with the evidences of chronic congestive heart disease The main disease from which the patient suffered however was incorrectly considered to be chronic myelogenous leukemia Evidence found at necropsy however indicated that the fundamental pathologic lesion was osteosclerosis with extensive extra medullary blood formation in the spleen liver, and lymph nodes

The most generally accepted view of the mechanism of the disease at present is that osteosclerosis is the primary disease and that the extra medullary hemopoiesis which is not normal during adult life gives rise to abnormal blood pictures Although the condition must be regarded as resembling chronic myeologenous leukemia from a clinical *standpoint as it is invariably fatal and the changes in the peripheral* blood resemble closely those seen in leukemia it is a disease of a fundamentally different nature

Myeloid Metaplasia of the Spleen—This is a rare condition described by Jackson and his collaborators in 1940 (*159*) It is allied to chronic myeloid leukemia but differs from it by the failure of the bone marrow to show leukemic changes the longer duration of life after the onset of symptoms and the *unfavorable* effect of the roentgen ray therapy

Etiology and Pathology—*The changes in the spleen* and bone marrow differentiate the condition from myelogenous leukemia In myeloid metaplasia the malpighian corpuscles are preserved and infarction is absent in the spleen Furthermore the bone marrow in myeloid metaplasia may be normal aplastic hyperplastic or fibrotic *but the changes never represent those seen in leukemia*

The cause of the disease is unknown but in 1941 Rawson Parker and Jackson (*176*) reported that the findings in this condition resembled those observed in chronic benzol poisoning which led them to investigate the occupational histories of their patients in their clinic with myeloid metaplasia It is of significance to note that of the six *all gave a history of exposure to certain industrial solvents including benzol and carbon tetrachloride* These observations suggest that exposure of some individuals to certain fat solvents may give rise to the clinical picture previously described by them as agnogenic myeloid metaplasia They conclude also that in the future it is quite likely that some patients with this condition will give no history of such an exposure and certainly many who will be exposed to such poisons will escape unharmed

In the opinion of Hutt Pinninger and Wetherley Mein (*176A*) it is more logical to regard myelofibrosis as a proliferative or neoplastic process which is closely related to the leukemias or to the primary lymph node tumors This theory would then consider the formation of fibrous tissue

Pathology —The characteristic findings on necropsy are the widespread presence of the characteristic tumors which have a yellowish green appearance Depending on the cell type these are either myeloblastomas or myelocytomas They have little stroma no reticulum and fair vascularity It is important to note that the leukemic infiltrations which occur act in the same manner as metastases and spread locally This tendency differs from ordinary leukemia as the invasiveness except for its close relation to bones and constant periosteal involvement closely resembles that seen in lymphosarcoma

The green tumor tissue may be distributed widely throughout the body The kidneys seldom fail to have it either diffusely placed or in nodules in the cortex Frequently the ovaries are greatly enlarged by the tumor Rarely is it present in the spleen liver the pancreas the adrenal glands or the bladder In all of these organs however the usual grayish leukemic infiltrations may be seen The pathologic picture therefore is that of a true neoplasm due to the unrestrained proliferation of either myeloblasts or myelocytes The exact nature of the green pigment is unknown but it is thought to be related to the porphyrins *(180)*

The skull and facial bones are affected in about 75 per cent of the cases Other bones are also involved in order of frequency as follows the sternum ribs vertebrae femora pelvis and tibiae The deposits are most pronounced in the subperiosteal regions but may also be found in the medullary or cortical portions of bone In about one half of the cases the pathologic process is found in the lymph glands According to Kemp and Williams *(179)* the viscera are involved in the following order of frequency kidneys liver lungs and pleura heart and pericardium pancreas intestine testes and spleen Tumors are not common in the brain and cord although various neurological signs such as a paraplegia may result from pressure of epidural masses or by obliteration of the blood supply by thrombosis of the vessels The bone marrow may be colored greenish but this is not usually the case It is usually hyperplastic grayish and may be semi liquid in consistency The usual finding is characteristic of acute myelogenous leukemia with myeloblasts predominating

Symptoms and Signs —As it is possible for the green tumor to invade all parts of the body the clinical manifestations may be most diverse In general it may be said that there are two main clinical pictures One is the so called classic syndrome which occurs usually in children The other is seen in adults and closely simulates acute or subacute myelogenous leukemia from which differentiation is difficult

In children the essential feature of the syndrome is a rapidly growing orbital tumor which invariably results in a striking ocular *protopsis* Varying degrees of blindness may be present and oculomotor palsies are sometimes apparent In association with this there is often cranial tumefactions lymphadenopathy and involvement of other bones

show no improvement It is their opinion, however, that an occasional patient derives definite benefit particularly when there is a severe thrombocytopenia or hemolytic anemia The results of splenectomy in an additional patient with this disorder has more recently been published by Seligman (*177B*) He concludes that removal of the spleen was not *catastrophic to the patient or the blood forming system* Furthermore, it is his opinion that the operation in well selected patients with severe thrombocytopenia may be of benefit

The reports of splenectomy in this condition indicate to me that although the procedure is much less harmful than we had been led to believe in the past yet it should be recommended with caution and then probably only when there is thrombocytopenia or evidence of an associated hemolytic anemia

Synonyms —Chloroleukemia aleukemic myelogenous chloroma

Definition —Chloroma in practically all cases, may be regarded as a variant of myelogenous leukemia in which a prominent feature is the deposition of greenish yellow tumor like masses in the skeleton especially the skull and orbital regions the lymph nodes, and the viscera

Etiology —This condition is rare as only 175 indubitable cases have been reported in the world literature up to 1937 It is undoubtedly true however that some cases have not been recognized during life as having a hematological disorder and others have been thought to have a myelogenous or lymphatic leukemia Unless a necropsy were done however the diagnosis of chloroma could not be made

The condition is almost twice as common in males as females This is illustrated by the 58 cases collected by Kandel (*178*) It has a distinct predilection for young persons and, in Kandel s series 43 of his 58 cases were younger than 18 years of age According to Kemp and Williams (*179*) the commonest age at which chloroma is seen is from five to six years

All evidence at present suggest strongly that chloroma is a variant of acute or subacute myelogenous leukemia although some authors still hold that the disease can also be associated with the lymphatic form of leukemia It is possible that confusion may result in deciding whether a patient has myelogenous or lymphatic leukemia because in the acute stage practically all of the cells are in the primitive state and difficulty is encountered in differentiating between lymphoblasts and myeloblasts Kandel states (*178*) With recent improvements in staining technic and better differentiation of the acute lymphoid and myeloid leukemias almost all of the recent cases of chloroma have been reported as cases of myeloid leukemia several standard texts to the contrary Hence the almost inevitable association of chloroma with myeloid leukemia should indicate clearly that chloroma is merely a variant of myelogenous leukemia with the myeloblast being the cell type of the tumor or infiltration which acts as an invasive neoplasm

According to Kemp and Williams (*179*) the radiological changes observed in the skeleton are not pathognomonic. They list the following conditions which must be considered in the radiological differential diagnosis:

1. Bone changes occurring in cases of myeloid and lymphoid leukemia which do not present the characteristic clinical features of chloroma, e.g. skull and orbital involvement.
2. Congenital syphilitic osteo-periostitis.
3. Secondary neuroblastoma (suprarenal primary).
4. Sub-acute periosteo-myelitis.
5. Scurvy.
6. Ewing's sarcoma.
7. Myelomatosis.

Diagnosis.—If a patient has the blood picture of myelogenous leukemia, especially of either the acute or subacute type, and bony and orbital tumors are present, the diagnosis of chloroma is probably correct. In the classic cranio-orbital syndrome without blood changes, other malignant growths of the orbit and cranium, Mikulicz's disease, osteomyelitis and abscess should be considered. With roentgenological evidence of bony involvement and in the absence of changes in the blood, scurvy and Ewing's tumor as well as essential xanthochromatosis with splenomegaly should be kept in mind. In the adult, when the clinical picture so commonly simulates that of myeloid leukemia with no distinguishing symptoms or signs to assist in the differentiation, the diagnosis is almost always made by the histologic examination of tissue.

The following patient, observed by me several years ago, shows that the course of the disease may be chronic in the adult and illustrates how difficult it may be to recognize the disorder during life: the patient was a 45-year-old married woman who had noticed a gradually increasing ease of fatigue, weakness and pallor over a period of two years. Two years after the onset it was found that her red blood cell count was 1.5 millions per cubic millimeter. She was treated with ventriculin and liver extract at this time, as the diagnosis was thought to be pernicious anemia. When seen by me shortly after the failure of the trial of antipernicious anemia therapy, the red blood cell count was 1.54 millions per cubic millimeter, the hemoglobin 35 per cent, and the white blood cell count 2250 per cubic millimeter. Some months after this the leukocyte count fell to 400 per cubic millimeter. The differential count showed that the neutrophils varied from 14 to 20 per cent and the lymphocytes from 62 to 81 per cent. Physical examination showed nothing except a barely palpable spleen and pallor. Sternal puncture yielded material which contained large mononuclear cells definitely abnormal but which could not be identified positively at that time. Six months later, just before the patient succumbed, the white blood cell count for the first time during

Invariably there is a rapidly progressive anemia which is refractory to all forms of therapy, and eventually the red blood cell count and the hemoglobin of the circulating blood fall to a low level. It is not common to have splenic enlargement, and hemorrhagic tendency is rare.

Although the blood is not infrequently typical of that found in patients with acute or subacute myelogenous leukemia, the syndrome of chloroma differs from this condition in several important features, as follows: bone is more likely to be involved in chloroma; there is slight, if any, tendency to bleed excessively, which is so common in patients with acute leukemia of any type; and the spleen is not enlarged as frequently as it is in acute myelogenous leukemia.

The second type of chloroma has been called chloroleukemia because it so closely simulates either the subacute or chronic form of myelogenous leukemia. Without the aid of a pathological examination it does not seem possible in most cases to foretell the diagnosis of chloroma. In most instances of this type of chloroma the clinical diagnosis is myelogenous leukemia. The clinical picture is the occurrence, usually in an adult, of a progressive pallor and other symptoms of an anemia associated with a rapid fall in the hemoglobin and red blood cell count of the peripheral blood. With this there is a loss of strength, varying amount of osseous pain and bony enlargement, and usually slight to moderate splenomegaly and lymphadenopathy.

Blood Examination.—In 52 cases reviewed by Kandel (*178*), eight had a leukocyte count of less than 6000 per cubic millimeter, in 13 the count was between 6000 and 15 000 per cubic millimeter, and in 31 it was over 15 000 per cubic millimeter. The white blood cell counts of the entire group varied from 310 to 299 000 per cubic millimeter. The percentage of myeloblasts varied from 0 to 97 per cent, with an average of about 50 per cent. In many cases it was not possible for those who examined the blood to identify the nature of the primitive type of cell definitely. In such cases these cells were called undifferentiated cells, hemohistioblasts and stem cells. The red blood cell count in the advanced stages may be in the vicinity of 1.0 million red blood cells per cubic millimeter and the hemoglobin from 20 to 30 per cent. Usually the color index is about 1. The anemia is practically always of the normochromic, normocytic or slightly macrocytic type.

Roentgen Ray Examination of the Bones.—The roentgenological examination is of assistance in the diagnosis in some cases, but the findings are variable. The most common change is a periosteal elevation which may be either lamellated and therefore simulate the appearance of scurvy, or ossified and resemble Ewing's tumor. In some cases there may be radiating spicules of ossifying material perpendicular to the shaft which produces a picture simulating that of osteogenic sarcoma. In some instances there have been multiple sharply punched out areas in the skull closely resembling multiple myeloma or metastatic carcinoma.

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the illness rose to 33 000 per cubic millimeter and 95 per cent of the white cells in the circulating blood were large mononuclear cells which were identified as myeloblasts At necropsy it was found that the usual bone marrow was replaced in many of the bones with a greenish type of tissue suggesting a chloroma There was gross evidence of metastases of this malignant process to the left kidney the liver and the skin The cells of this greenish tissue were large mononuclears which were considered by the pathologist to be myeloblasts There was neoplastic transformation and infiltration of all the bone marrow the lymph nodes skin larynx spleen liver kidneys and rectum

Prognosis and Treatment —The disease in both of its clinical forms uniformly runs a rapid course and death usually occurs in from a few weeks to 18 months Repeated blood transfusions may be of some help and are indicated at any time the red blood cell count and hemoglobin falls to a level where significant symptoms are present Treatment with the roentgen ray is of no use and in many cases the results are unfavorable Arsenic has been recommended in the form of neoarsphenamine injections but there is no evidence that such therapy is beneficial

MULTIPLE MYELOMA

Synonyms —Multiple myelomatosis plasmacytoma Kahlers disease

Definition —Multiple myeloma is a malignant tumor of the bone marrow usually terminating fatally usually within one or two years after the onset arising in the cells of the hematopoietic system characterized by multiple destructive lesions of the skeletal trunk pathological fractures anemia and often by the presence of Bence Jones protein in the blood and urine The condition rarely occurs before the age of 40 years and is twice as common in males as females The average age of a group studied by Ghormley and his associates *(181)* was 54 years

History —In 1848 Henry Bence Jones on examining the urine of a patient discovered that it contained a substance which precipitated on heating but cleared on boiling and reprecipitated on cooling *(182)* Subsequently when a necropsy was performed on the patient he observed that the ribs cut with ease as did the vertebrae In 1846 Dalrymple *(183)* described the gross and microscopical characteristics of the diseased bone in such cases and recognized that it was replaced by nucleated cells He suspected that the process was neoplastic in nature A classical clinical description of the disorder was given in 1850 by MacIntyre *(184)* The description of the condition under the name of Multiples Myelom was first published by von Rustizke in 1873 *(185)* In 1889 Kahler *(186)* described the four classical features of the condition namely bone pain deformation and abnormal fragility of bone cachexia and the presence of Bence Jones proteinuria which led to the disease being designated as Kahler s disease The increase in the

plasma proteins of the blood was first observed by Ellinger (*187*) In 1939 the initial electrophoretic observations were made on the plasma proteins by Longsworth Shedlovsky and MacInnes (*188*)

Pathology—It is now generally agreed that the condition is a neoplastic process arising from the cells of the hematopoietic system As long ago as 1900 James Homer Wright stated that the distinctive cells of this tumor resembled the plasma cell closely Concurrence with this view was expressed by Christian in 1907 (*189*) There is now a general tentative acceptance of the idea that the condition may be regarded as a subleukemic plasma cell leukemia

Multiple myeloma cells as they have been called vary in size from 15 to 30 microns with a cytoplasm which stains deeply basophilic It should be emphasized that the cytoplasm is basophilic and bright blue not blue green as in the true plasma cell when stained with Wright s stain In some instances there may be a light perinuclear staining zone and in this respect they resemble the lymphocyte The nucleus is round or oval and usually measures 5 to 7 microns in diameter It has as its most outstanding feature a large conspicuous nucleolus The chromatin is usually arranged either in fine or coarse strands rarely in dense masses The spoke like arrangement typical of the true plasma cell is not present

The progenitor of the myeloma cell is unknown as is true also of the plasma cells Possible sources of the myeloma cell which have been mentioned are the myeloblast hemocytoblast the reticulo endothelial cell lymphocyte megakaryocyte and osteoblast According to Ghormley and his associates (*181*) it seems most likely that the myeloma cell is derived from the reticulo endothelium This and the possibility that such a cell may arise from the lymphocyte are the two beliefs which are most favorably considered at present Some speak of the cells as plasma cells but inasmuch as they are not identical with them it is perhaps most accurate to refer to them for the present as myeloma cells

The tumors are characteristically multiple and are confined almost exclusively to the sites of the red marrow namely the ribs the sternum the spine clavicles or the extremities about the shoulder or pelvic girdle They usually range in size from that of a pea to a hazelnut The tumors cut readily with a knife as the outer shell of bone is characteristically thin The tumor itself is made up of a dark gray or red mass of gelatinous material which bleeds very readily Microscopically it is composed of the plasma or myeloma cells eosinophils fat cells and giant cells The tumors are rich in blood vessels which accounts for the ease with which they bleed and also for the fact that they are sometimes observed to pulsate It is not characteristic of the disease for the growths to metastasize to other tissues than bone but occasionally collections of myeloma cells are found in the liver spleen lymph nodes the kidneys ovaries testes and adrenals

the illness rose to 33 000 per cubic millimeter and 95 per cent of the white cells in the circulating blood were large mononuclear cells which were identified as myeloblasts At necropsy it was found that the usual bone marrow was replaced in many of the bones with a greenish type of tissue suggesting a chloroma There was gross evidence of metastases of this malignant process to the left kidney the liver and the skin The cells of this greenish tissue were large mononuclears which were considered by the pathologist to be myeloblasts There was neoplastic transformation and infiltration of all the bone marrow the lymph nodes skin larynx spleen liver kidneys and rectum

Prognosis and Treatment—The disease in both of its clinical forms uniformly runs a rapid course and death usually occurs in from a few weeks to 18 months Repeated blood transfusions may be of some help and are indicated at any time the red blood cell count and hemoglobin falls to a level where significant symptoms are present Treatment with the roentgen ray is of no use and in many cases the results are unfavorable Arsenic has been recommended in the form of neoarsphenamine injections but there is no evidence that such therapy is beneficial

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Laboratory Findings—Bence Jones Protein—The presence of this type of protein in the urine which occurs in only a portion of the cases is of great diagnostic importance In summarizing the literature Adams and his associates (*193*) report the incidence of Bence Jones proteinuria as varying from 8 to 87 per cent A reasonable estimate based on my own experience is that protein of this type occurs in the urine in 50 to 65 per cent of the patients with multiple myeloma

Its presence in connection with the diagnosis has been emphasized so much however that some physicians are reluctant to consider the diagnosis of multiple myeloma in its absence It should be kept in mind that about one third of the cases do not have this type of protein in the urine as indicated by careful tests in which heating in a water bath increasing the concentration of sodium chloride and insuring a proper acidity of the urine are employed This type of protein precipitates at temperatures of 50 to 60 degrees C further heating causes it to go into solution at about the boiling point and on cooling it reappears Needless to say a superficial examination of the urine is not likely to disclose it It occurs occasionally in the urine of patients with leukemia and polycythemia I have observed it recently in a patient in whom biopsy of a lymph node disclosed lymphosarcoma It must be remembered that these exceptions are rare and that the presence of Bence Jones protein in the urine usually means that the patient has multiple myeloma

As discussed under the section of pathology the function of the kidney may be impaired possibly by the increased viscosity of the blood and due to the deposition of the Bence Jones protein in the glomerular capillaries For this reason in over one half of the cases there may be albumin in the urine and often red blood cells white blood cells and casts present In some there is a seriously impaired renal function as evidenced by an increase in the non protein nitrogen of the blood above normal limits

The Nature of Bence Jones Protein—This protein is known to be of variable composition and is distinct from the normal protein contained in the plasma Its true nature origin and physiology are still incompletely known Its origin is not exogenous and the very fact that so much is excreted in some cases precludes the possibility that it is a metabolite formed by the tumors throughout the body The generally accepted values for the molecular weight are 35 000 to 27 000 According to Devine (*194*) it appears more likely that it arises from either (a) the partial breakdown of normal protein of higher molecular weight or (b) that it results from some hindrance to the complete synthesis of a similar normal protein It is possible in accordance with these suggestions that it is derived from normal serum globulin by the latter being split into three particles of equal size or that it is formed from a deranged synthetic mechanism which would otherwise produce normal plasma or some other type of proteins

Hyperproteinemia—There may be a pronounced hyperproteinemia as indicated by a plasma protein level which may reach 10 grams per 100 cc

The *nephritis* of multiple myeloma cannot be regarded as a true nephritis or nephrosis as hypertension generalized edema, or retinitis are not observed It has been claimed by Bell (190) that the renal impairment is attributable to protein casts found in the renal tubules Forbus and his associates (191) contended that renal injury results from the toxic action of Bence Jones protein on the kidney which evokes a foreign body reaction In a recent study by Armstrong (192) it is concluded that there is no simple and obvious relation between the impaired renal function, the age of the patient the duration of the disease, the presence or degree of the Bence Jones proteinuria the changes in the circulating blood or the quantity of abnormal serum protein While he is unable to conclude definitely it is his opinion that the findings suggest glomerular as well as tubular changes

Symptoms and Signs —The symptoms are often of a diverse nature and are frequently present in patients for 10 to 12 months before a physician is consulted The most common chief complaint is pain in the back and in many instances this may be the sole symptom As a result in some cases the erroneous diagnosis of osteo arthritis of the spine or neuritis is sometimes made At first the pain may be vague annoying and intermittent Frequently especially in the early stages of the disease it may have relatively long periods of remission In other patients there may be mild and shifting pains of a rheumatic nature referred to the chest and extremities

The next most common presenting symptoms are weakness and loss of strength Other manifestations may be an anemia with a progressive pallor dyspnea and palpitation and ease of fatigue loss of weight evidences of pathological fractures and rarely the observation by the patient that a tumor of bone is present

As the disease progresses it is not rare to have compression fractures of the spine with pressure on the spinal cord and a resultant spastic paraplegia Other symptoms due to the same cause are intercostal neuralgia and radiculitis Physical examination usually reveals a patient who is emaciated and uncomfortable from pain in the back On the other hand the condition is sometimes discovered at a time when the patient appears to be in good health and its presence has been detected only as a result of finding Bence Jones protein in the urine or from observation of the characteristic lesions in the skull or other bones The patient may have become aware of the tumors from tenderness or noting a lump on a bone or from symptoms arising from spontaneous fractures The swelling when present is usually small ordinarily not being larger than the end of the thumb As a result of destruction of a vertebra it is not unusual to have a thoracic deformity The liver is palpable in about 25 per cent of the patients and the spleen in less than 10 per cent In neither instance is there gross enlargement Rarely have I observed an abnormal tendency to bleed but a secondary thrombocytopenic purpura may occur

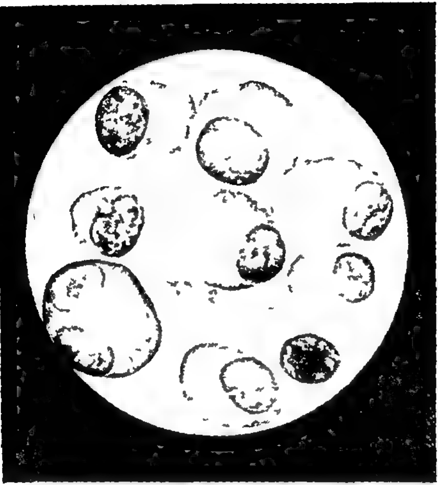

PLATE VIII *Multiple Myeloma (Plasmocytoma)*—Direct smear of material aspirated from the sternum and stained with Wright's stain. The patient, a man aged 46, complained of dull pain in the thoracic and lumbar regions of the spine of about four months duration. There was a moderately severe normochromic anemia, conspicuous rouleaux formation of the erythrocytes, and an essentially normal leukocyte picture. Plasma cells were not found in the peripheral blood. Roentgenograms revealed osteoporosis without osteolytic lesions. In the diagnosis of multiple myeloma the most important procedure is sternal marrow aspiration. The characteristic cells, which tend to occur in clumps and may outnumber all other myeloid elements, are large with eccentric nuclei possessing deeply staining, heavily massed chromatin, often with nucleoli, and a variable amount of intensely basophilic, coarsely textured cytoplasm. Cells with multiple nuclei are commonly found. Differentiation from the normal plasma cells of the marrow is made by the greater size of the neoplastic elements and the immaturity of their nuclei as well as by their increased numbers. The field illustrated contains, in addition to myeloma cells, a metamyelocyte and a normoblast. Wright's stain. Magnification 960.

TABLE XXXIX

SUMMARY OF DATA CONCERNING CONSTITUENTS OF BLOOD IN ENTIRE SERIES (*181*)

Investigation	*Estimations*	*Abnormal Results*		
		Type	*Cases*	*Per Cent*
Albumin Globulin Ratio	23	Reversed	13	56.5
Uric Acid	6	Elevated	4	66.6
Blood Cholesterol	5	Reduced	3	60.0
Blood Calcium	48	Elevated	0	20.8
Blood Phosphorus	42	Elevated	4	9.5
Blood Phosphatase	22	Elevated	4	18.1
Serum Sulfate	16	Elevated	5	31.2
Serum Protein	20	Elevated	10	50.0
Blood Urea	57	Elevated	21	36.8
Sedimentation Rate	29	Elevated	23	79.3
Blood Creatinine	9	Elevated	5	55.5
Bence Jones Protein in Urine	112	Positive	68	60.7

One estimation listed per case
(Ghormley, Pollock and Hall. Courtesy *Surgery, Gynecology and Obstetrics*.)

of blood and even figures much higher have been reported. The increase is always due entirely to a higher globulin level. In many cases, therefore, the albumin globulin level is reversed. Spontaneous clumping of the erythrocytes which has sometimes been called auto agglutination is present in some cases. This accounts for the striking rouleaux formation and an accelerated blood sedimentation rate. The spontaneous clumping has been attributed by some to the high level of the globulin. As a result of this tendency to abnormal agglutination it may be difficult to enumerate the erythrocytes in the hemocytometer. Also the blood films are usually of poor quality, resembling those which have been made on cover slips from which the grease has not been completely removed. The inorganic blood phosphates are usually normal but the blood calcium is often increased to levels of 12 to 16 milligrams per 100 cc of blood.

A resumé of the frequency with which various chemical changes occur in the blood and urine has been compiled by Ghormley and associates (*181*).

Electrophoretic Studies in Multiple Myeloma.—Since the initial observations of Longsworth, Shedlovsky and MacInnes (*188*) in 1939 the most comprehensive studies of changes in the electrophoretic patterns in multiple myeloma have been made by Gutman and his associates (*195*) and by Moore *et al* (*196*). If the elaborate apparatus and experienced technical assistance is available for the determination of this new type of laboratory procedure it is undoubtedly of great assistance in the diagnosis of multiple myeloma. The reader is referred to the study of Adams and his associates (193) for the details concerning the accuracy of such studies in the diagnosis of this disorder. They state that in 29 cases of diffuse plasma cell tumor the electrophoretic patterns were abnormal in all. In

one case of solitary myeloma of the antrum with an associated infection the patterns were normal except for the changes commonly encountered in such an infection It appears therefore to be a reliable diagnostic procedure to employ in patients suspected of having a multiple myeloma

Sternal Puncture —There is no question but what sternal puncture with aspiration of a small amount of marrow provides a simple and highly accurate method for the diagnosis of this condition In some instances the diagnosis is impossible without information furnished by this procedure One satisfactory technic is to place a small amount of material aspirated from the marrow cavity of the sternum into a paraffin lined test tube to which has been added a small amount of heparin Films are made from this and stained with Wright s stain If the nucleated cells are scant in the material the fluid can be centrifuged and films made of the buffy layer

According to Beizer Hall and Giffin (*197*) plasma cells make up less than 1 per cent of the white blood cells in the material obtained from a normal person by sternal aspirations and these cells are identical with those found normally in the circulating blood Myeloma cells were found by these authors to make up 20 per cent or more of all of the cells of the marrow in patients with multiple myeloma This form of cell they describe as having the following characteristics The cytoplasm is abundant deeply basophilic and contains a moderate sized concentrically placed nucleus having coarse chromatin and a very large nucleolus A perinuclear zone may occur but it is not common They concluded that in their cases it was possible to trace cells which ranged in appearance from those identical with plasma cells seen in the blood and normal marrow to the characteristic myeloma cell They have not found a typical myeloma cell to be present in the bone marrow in any other conditions than multiple myeloma

The consistent absence of multiple myeloma cells from the material obtained by repeated and satisfactory sternal punctures is strong evidence against the diagnosis of multiple myeloma Comprehensive reviews of the bone marrow findings in patients with this disorder are given by Diggs and Sturidge (*198*) and by Bayrd (*199*) Additional discussion of the *bone marrow changes in this disorder is given in the chapter* on sternal puncture (page 1109)

Attention should be directed to the observation by Fadem and McBirnie (*200*) that an increase in the number of plasma cells varying from 5 4 to 23 6 per cent which is well above the 3 per cent level given by Waldenstrom as diagnostic of primary plasmacytic disease (*201*) may occur in other conditions than primary plasma cell disease These values above 3 per cent were observed in patients with Hodgkin s disease lymphosarcoma acute monocytic leukemia a primary "refractory anemia a hiatal hernia and a papilloma of the bladder They warn that before a diagnosis is made of a primary plasmacytic disease from the findings in

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the bone marrow, other diagnostic criteria should be taken into consideration

Blood Examination —The most important changes which occur in the blood of patients with multiple myeloma are (1) anemia (2) excessive rouleau formation and (3) the presence of myeloma cells In addition there may be (4) immaturity of the red blood cells and leukocytes or (5) a slight lymphocytosis and (6) occasionally an eosinophilia

Most patients with this condition have a moderate anemia of the normocytic, normochromic variety Rarely is it absent when the disease is advanced In some instances, it is severe and of the macrocytic type suggesting the blood picture of pernicious anemia In a group of 56 cases studied by Morissette and Watkins (202) the hemoglobin percentage of the peripheral blood averaged 8 8 grams (55 per cent on the basis of 15 6 grams equals 100 per cent) in six it was over 12 grams (73 per cent) and in eight it was less than 6 grams (37 per cent) In three cases the erythrocytes numbered more than 4 0 per cubic millimeter and in 11 less than 2 0 million per cubic millimeter, the average erythrocyte count was 2 780 000 per cubic millimeter The color index was almost always approximately 1 0 The anemia in these patients has been attributed to the replacement of red blood forming elements of the bone marrow by myelomatous tissue to a hypothetical toxic inhibitory effect on the maturation of the red blood cells and in some cases to renal failure which occurs in a fair number of cases with this condition In general it may be said that the anemia is probably accounted for on the basis of infiltration of the bone marrow with myelomatous cells and should therefore be regarded as a myelophthisic variety On the other hand it appears likely that renal failure may contribute to the degree of anemia in a certain percentage of patients with the disorder In any event all observers are in accord with the statement that the anemia regardless of its cause is not benefited by either iron or liver medication

Excessive rouleau formation and autohemoagglutination have been discussed under the heading of Hyperproteinemia " as there appears to be a definite causal relationship between the increased level of the globulin of the blood stream and these changes This change is often apparent in wet preparations because the clumping may be so great as to prevent an erythrocyte count and in dried blood films the excessive rouleaux formation gives the impression that it has been made on a cover slip from which the grease has not been completely removed As has been previously stated there is an increased sedimentation rate in this condition which is probably associated with the abnormal clumping of red blood cells which causes them to settle more rapidly Hence the increased globulin content of the circulating blood the excessive clumping of the red blood cells and the increased sedimentation rate all have a causal relationship

Of some importance from the standpoint of diagnosis is the presence of myeloma cells or atypical plasma cells in the circulating blood in this condition There is no question but what they are present in about three quarters of the cases although their presence is not detected in most instances unless an intensive search is made for them with the low power of the microscope by an expert hematologist By covering a large surface of the blood film with the lower power these cells may be located and then positively identified by means of the oil immersion magnification The histologic characteristics of the myeloma cells have been described in the paragraphs dealing with sternal puncture It is usually possible to trace in the bone marrow and also the circulating blood intermediate

Fig 66—Blood film showing myeloma cells (× 1120) in the circulating blood of a patient with multiple myeloma a myeloma cell with a nucleus of sieve like pattern, rouleaux formation is present b typical myeloma cell with a coarse chromatin net work rouleaux formation is more pronounced than in a (Morissette Leopold and Watkins courtesy *Proceedings Staff Meeting Mayo Clinic*)

stages between myeloma cells and plasma cells According to some observers it has been possible to detect either myeloma cells or plasma cells or both in the circulating blood of as many as 73 per cent of all cases of multiple myeloma (*202*) Hence if these cells have been positively identified in the peripheral blood by an experienced hematologist it is an important assistance in recognizing cases of this type

A few immature leukocytes in the form of young neutrophils and even myelocytes are recognizable in about one half of the cases Normoblasts may also occur but they are found only occasionally Polychromatophilia is relatively common and proportional to the severity of the anemia

It has been demonstrated that a slight to moderate lymphocytosis occurs in some patients with this disease but it is not common It is not therefore of value from the standpoint of diagnosis In one group of patients (*202*) the differential count showed a percentage of 35 or more

the bone marrow other diagnostic criteria should be taken into consideration

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Summary of Laboratory Findings —A résume of the frequency of occurrence of various laboratory findings in 61 cases of multiple myeloma is given by Adams and his associates (*193*) as follows Electrophoretic abnormalities 100 per cent increased number of plasma cells in the sternal marrow 86 per cent anemia 86 per cent x ray changes 86 per cent hypoalbuminemia 84 per cent hyperglobulinemia 67 per cent rouleau formation 60 per cent renal insufficiency 57 per cent hyper proteinemia 52 per cent elevated alkaline phosphatase 48 per cent Bence Jones protein 47 per cent azotemia 46 per cent anticomplementary Wassermann 25 per cent plasma cells in the peripheral blood 25 per cent hypercalcemia 24 per cent hyperphosphatemia 22 per cent and leukopenia 11 per cent

Diagnosis —The recognition of this condition is sometimes difficult and the true diagnosis may not be made until necropsy is performed Originally Geschickter and Copeland (*205*) gave 6 cardinal diagnostic clinical manifestations of the disease any two of which they thought were usually present These were (1) multiple involvement of the skeletal trunk in an adult (2) pathological fracture of a rib (3) excretion of Bence Jones bodies in the urine (4) characteristic backache with signs of early paraplegia (5) an otherwise unexplained anemia and (6) chronic nephritis with nitrogen retention low blood pressure and high serum proteins

It has been emphasized however by Beizer Hall and Giffin (*197*) that cases have been reported in which none of these changes were present and several other features have been described frequently enough to be important These are (1) hyperproteinemia with reversal of the albumin globulin ratio (2) hypercalcemia with normal or high serum phosphorus (3) *evidence of hemagglutination in the counting chamber* or blood films and (4) the occurrence of an anticomplementary reaction when a complement fixation test is carried out Another may be added namely that there is an increased sedimentation rate which is probably associated with the autoagglutination It is obvious that none of these tests are pathognomonic Nevertheless the occurrence of a sufficient number of them in the same patient should always suggest the possibility that the disease is present

The best advice to follow for the detection of multiple myeloma in patients is given by Adams and his collaborators (*193*) It may be epitomized as follows (1) if hyperproteinemia or hyperglobinemia are detected electrophoretic studies should be carried out (2) attention should be given to the possible diagnostic significance of rouleaux formation and the bright blue color of blood films when stained with Wright s stain (3) in the presence of any unexplained anemia do a sternal puncture or biopsy if necessary (4) search all urine specimens containing albumin for Bence Jones protein (5) determine the level of the serum

lymphocytes in 25 of 56 cases and one of more than 45 per cent in nine cases. The cause for this moderate lymphocytosis is not definitely known. Some have suggested that it may be associated with encroachment of the myeloma cells on the lymphoid tissue and others have considered that it is concerned with the possible genetic relationship between the plasma cells and the lymphocytes.

Not infrequently there is a moderate eosinophilia present and occasionally this may exceed 10 to 15 per cent; in rare instances it may be greater than 40 per cent. The exact significance of eosinophils of mild or excessive degree is not known and as it occurs in other conditions even more frequently it is not of diagnostic value.

The platelets are usually normal in number but there may be a thrombopenia. With the invasion of the bone marrow by cells which are probably malignant in nature, a process similar to that which occurs in myelogenous and lymphatic leukemia, it might be expected that the platelets would decrease as a result of a diminution in the number of megakaryocytes of the marrow. Two cases are reported by Rosenthal *(203)* in which a secondary thrombopenic purpura occurred. In one the condition became manifest after removal of the spleen and in the other the multiple myeloma was detected by sternal puncture.

A case of multiple myeloma with liver infiltration and a low prothrombin purpura is reported by Schindler *(204)*. The author states that in about one half of the cases of multiple myeloma there is an infiltration of the soft tissues, particularly the liver, spleen and kidneys, which are invaded by typical round cells, closely resembling plasma cells. In the case presented an infiltration was present to such a degree that the resultant liver damage caused was responsible for a low blood prothrombin which in turn caused spontaneous bleeding. As was to be expected the low blood prothrombin was not affected by the injection of 2 methyl 1 4 naphthoquinone.

Roentgen Ray Examination.—Although osteolytic lesions are traditionally considered to be typical of multiple myeloma, the disease may occur in the complete absence of such lesions. The only abnormality detectable in the x rays may be a generalized decalcification or osteoporosis. It is stated by Adams and his associates *(193)* that the commonest (although far from diagnostic) x ray change is one of widespread osteoporosis involving the entire skeleton. In rare instances a patient may be suffering from multiple myeloma and not display x ray changes of any type. In general the characteristic changes are punched out areas with sharp edges most commonly occurring in skull, vertebrae and ribs without surrounding osteoblastic changes. Such findings cause the roentgenologist to suggest at once the diagnosis of multiple myeloma. It is not possible, however, to distinguish these changes from the multiple metastatic lesions of carcinoma on the basis of the x ray changes alone.

ones to the growth inhibiting action of the drug It produces selective suppression of growth of these abnormal cells in three weeks to three months In a more recent study by Rundles Dillon and Dillon (*209*) they state that as the plasma cell growth is inhibited by means of urethane in patients with multiple myeloma the abnormal serum protein components even those generally found not to represent Bence Jones proteinemia are reduced or may virtually disappear This change parallels the reduction or disappearance of Bence Jones proteinuria Not only do these observers believe that urethane curtails the growth of plasma cells but according to them when the drug is withdrawn the number of plasma cells in the bone marrow decreases along with other evidence of regression of the disease They believe therefore that with the withdrawal of the drug the growth of plasma cells are inhibited anew because as a result of the prolonged use of the chemical the abnormal proliferating cells have become dependent on it

Urethane is given in the form of 5 grain (0 3 gram) enteric coated tablets three times daily before during or after meals depending on how well it is tolerated by the patient The total dose is increased 5 grains (0 3 gram) daily to the point of tolerance but usually not exceeding a total dose of 45 grains (3 0 grams) a day In some instances however the patient has been able to tolerate as much as 60 grains (4 0 grams) daily In about three weeks a reduction in the leukocyte count is noted Care should be used in administering the drug When relief is obtained or when the white blood cell count falls below 4000 per cubic millimeter the drug should be discontinued for a few days and then given in a maintenance dose of about 1 0 to 1 5 grams daily Some patients tolerate the preparation well in others it is difficult to administer it in sufficient quantities to obtain satisfactory results There is no doubt however but what this form of treatment has a palliative value and warrants a trial in all patients with the disease It has the merit of simplicity and promises at least temporary relief in a majority of patients

Stilbamidine (4 4 stilbenedicarboxamidine) was introduced as a treatment of multiple myeloma in 1946 by Snapper (*210 211*) because it had been used effectively in treating leishmaniasis and both diseases were accompanied by hyperglobulinemia After treating 35 patients with the drug Snapper concluded that 80 per cent had relief from pain but warned that at best the disorder is only controlled temporarily relapses occur and the increased globulin in the serum is not influenced Furthermore in patients with kidney damage a condition commonly encountered in myeloma it is dangerous to give the drug as it may exert an unfavorable influence on renal function In addition in a majority of the cases a dissociated anaesthesia of the trigeminal branches occurs several months after the treatment is terminated

It is of interest to note that Snapper observed basophilic alterations in the multiple myeloma cells following treatment with the drug He re

calcium inorganic phosphorus and alkaline and acid phosphatase in patients suspected of having the disease, and (6) careful investigation with the diagnosis of multiple myeloma in mind, of all patients who have osteolytic lesions of bone or osteoporosis In an excellent study of 51 cases of plasma cell myeloma Meacham (*205A*) emphasizes that among other diagnostic criteria, diffuse osteoporosis is commonly present It is usually associated with localized osteolytic lesions but in some instances it may be the sole evidence of bony involvement This observer also properly emphasizes that the anemia may be microcytic in type and hence lead to diagnostic error

Treatment and Prognosis—After an average duration of 18 to 24 months, the disease always terminates fatally In patients who have solitary nodules however the outlook is much more favorable It has been reported by Gootnick (*206*) that the duration of life in such patients after the onset of symptoms, was seven years when treated with x ray

In some cases with the usual generalized form of the disorder, the course is interrupted by spontaneous remissions which may delay the fatal outcome for several months It is stated by Garland and Kennedy (*207*) that survivals as long as seven years have been recorded following roentgen therapy They report a patient with multiple myeloma, treated with x ray, who is still living after nine years He is clinically well although there is extensive evidence of the disease process in the skeleton There is no curative form of therapy but a good deal can be done for the relief of pain and possible prolongation of life Transfusions should be given to maintain the blood approximately within normal limits Orthopedic measures are indicated in some patients especially those with compressed vertebrae as striking relief usually follows

The following forms of treatment should be given consideration as palliative measures (1) Roentgen therapy which often gives striking relief of pain in the back and is well worth a trial when the pain and discomfort are attributable to bony involvement (2) Radioactive phosphorus has been employed as another form of irradiation with about the same results as x ray as reported by Lawrence and Wasserman (*208*) Their conclusions based on a review of the literature and their own experience in treating 24 patients with radioactive phosphorus and strontium was that this form of therapy was useful in some cases and it is their suggestion that a trial of isotope therapy in combination with stilbamidine or urethane be given The length of life in their group of 24 patients was approximately three years after the onset of symptoms which is better than average

Urethane has been advocated as a form of therapy in this disorder especially by Loge and Rundles (*133*) The rational of this form of treatment is that the abnormal granulocytes of myelocytic leukemia and the proliferating plasma cells in multiple myeloma are the most sensitive

ones to the growth inhibiting action of the drug It produces selective suppression of growth of these abnormal cells in three weeks to three months In a more recent study by Rundles Dillon and Dillon (*209*) they state that as the plasma cell growth is inhibited by means of urethane in patients with multiple myeloma the abnormal serum protein components even those generally found not to represent Bence Jones proteinemia are reduced or may virtually disappear This change parallels the reduction or disappearance of Bence Jones proteinuria Not only do these observers believe that urethane curtails the growth of plasma cells but according to them when the drug is withdrawn the number of plasma cells in the bone marrow decreases along with other evidence of regression of the disease They believe therefore that with the withdrawal of the drug the growth of plasma cells are inhibited anew because as a result of the prolonged use of the chemical the abnormal proliferating cells have become dependent on it

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gards this as a specific alteration consisting of precipitates of ribonucleic acid conjugated with stilbamidine

He recommends that the drug be given intravenously or intramuscularly with an initial injection of 50 milligrams and a second one of 100 milligrams two days later followed by injections of 150 milligrams every other day until a total of 15 to 20 injections have been administered He warns that the drug should be given with caution to patients with impaired renal function and advises that better results are attained when the patient receives a diet low in animal protein The latter is recommended because he has found by test tube experiments that nucleic acid and arginine have a neutralizing effect on the medication

The reports concerning the efficacy of stilbamidine are not uniformly favorable It is concluded by Propp, Gorham and Kantor (*212*) that this treatment failed to relieve pain in three of five patients and that although pain disappeared in one patient the osteolytic lesions progressed as shown by x ray They did not observe an arrest or remission in the course of the disease in any of five patients Trigeminal neuropathy with severe discomfort persisted for six months following treatment in one patient Four patients with multiple myeloma did not receive any degree of persistent relief when treated with stilbamidine by Baker and Casterline (*213*) and there was no evidence that the progress of the disease had been checked

In general it appears that stilbamidine is not the treatment of choice in such patients I have refrained from using it because of the unfavorable reports that the complications may be serious and uncomfortable and other forms of readily available therapy are more likely to accomplish the desired results

ACTH and Cortisone —These preparations have been used by Bethell (personal communication) in the treatment of six patients with multiple myeloma with uniformly good results for periods varying from a few weeks to a few months It is too early to make a definite statement concerning their efficacy but in all likelihood they will prove to be as effective or more so than other forms of therapy in producing temporary remissions

In summary in addition to blood transfusions and orthopedic measures urethane x ray radioactive phosphorus and ACTH and cortisone may be used to relieve the pain associated with multiple myeloma In almost all instances the relief is worth while but it is difficult to demonstrate that any one of these forms of therapy prolong life appreciably Stilbamidine may give relief but it is inferior to the other therapeutic measures mentioned above because it is less regular in its action and may have an unfavorable effect on the kidneys and trigeminal nerve

Relation of Multiple Myeloma to Plasma Cell Leukemia and Extramedullary Plasmacytomas It is now accepted by many that plasma cell

new growth may occur in the body in three forms all having in common plasma cells as the type cells involved They are (1) *plasma cell tumors involving* primarily bone or *multiple myeloma* which has been regarded as a subleukemic plasma cell leukemia (2) *plasma cell leukemia* with a diffuse infiltration of plasma cells in the bone marrow the lymph tissues the liver and spleen with or without an increase in the number of these cells in the circulation and (3) *extramedullary plasma cell tumors* arising in other tissues than bone

Multiple myeloma which has been already described resembles leukemia in a number of features These points suggesting that multiple myeloma is leukemic in nature have been summarized by Rubinstein (*214*) as diffuse infiltration with multiple myeloma cells without bone involvement extramedullary involvement of various organs as the spleen kidneys and others invasion of the circulating blood with leukemia cells increased uric acid content of the blood and elevated basal metabolic rate which is seen also in leukemia occurrence of myeloma in youth and symptomatology of myeloma at times not referrable to the osseous system In the opinion of Rubinstein (*214*) the difference between myeloma and leukemia is merely one of incidence that is what is rare in one disease is common in the other and vice versa He concludes by stating that multiple myeloma is probably a leukemia of plasma cells usually of the aleukemic type

It is of interest to note that multiple myeloma may develop in a patient with polycythemia just as in a certain number of instances myelogenous leukemia may occur as a complication of this disorder Four cases of polycythemia and definite myeloma have been reported by Lawrence and Rosenthal (*215*) and they have found two similar cases in the literature and in addition two cases of polycythemia with Bence Jones proteinuria in the literature

Plasma Cell Leukemia—A number of cases of plasma cell leukemia have been reported in which all of the important changes characteristic of the disease such as a high white blood cell count and leukemic infiltrations in various tissues have been present Such cases have been reported by Patek and Castle (*216*) by *Reiter and Freeman* (*217*) by Hill and Hawn (*218*) and others A case of plasmacytic leukemia in a male age 55 years who presented the clinical features of an acute or subacute leukemia with death in about four months from onset of symptoms is reported by Hill and Hawn (*218*) Biopsy and necropsy findings were those of leukemic infiltration of the spleen lymph nodes and bone marrow by plasmocytes or their immediate precursors The red blood cell count was possibly inaccurate on account of spontaneous agglutination and rouleau formation but is recorded as 2 15 millions per cubic millimeter with a hemoglobin estimation of 4 9 grams The white blood cell count on admission was 29 300 per cubic millimeter with 22 per cent

plasmocytes A patient with diffuse plasma cell infiltration of the viscera of the type usually seen in plasma cell leukemia, but without a significant number of plasma cells in the blood strain, is reported by Stark and Amidon (*219*)

Extramedullary Plasmacytomas —Although plasma cell tumors usually involve bone and are designated as multiple myeloma it is known also that they may arise as extramedullary tumors A comprehensive review with many references is given by Hellwig (*220*) In 127 published cases which include all those reported between the years 1905 and 1942 he found that in 63 the tumors originated in the air passages, in 47 in the conjunctiva in four in the lymph nodes and in 13 other organs as the pleura mediastinum spermatic cord thyroid gland ovary, intestines kidney, and skin It is concluded by Hellwig (*220*) that a plasma cell tumor may arise in almost any situation in the body and may behave as a simple benign growth or as a neoplasm of the most malignant type In his opinion localization and gross appearance of the growth seem to be more reliable criteria of the degree of malignancy than the histologic structure As long as the plasma cell tumor is localized and confined to soft tissues a clinical cure is possible by surgical removal or irradiation of the growth or a combination of both There is no therapy however which will prove effective after the tumor has invaded bony structures or spread to the lymph nodes Recently Switzer Moseley, and Cannon (*221*) have reported a case of extramedullary plasmocytoma involving the pharynx skin and lymph nodes This patient did not respond favorably to roentgen therapy and only transient improvement resulted from nitrogen mustard therapy The results of urethane therapy had not been determined when the article was published

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CHAPTER XVII

MALIGNANT LYMPHOMA

Introduction and Classification —Many general terms such as lymphoma and lymphoblastoma have been employed to include certain disorders of the lymphatic system which have at least two easily recognizable characteristics These are first a fatal progressive painless non tender tumor like enlargement of the lymph nodes and second a histologic picture which results from the multiplication of one or more elements normally present in these nodes eventually leading to a destruction of their nodal architecture The term malignant lymphoma at least has the advantage of being non committal as to etiology and also indicates the progressive nature of the disorder

Classification —The classification of the lymphoma group is confused because 1 the clinical characteristics of each subtype are often not distinctive enough to permit a clean cut differentiation and hence the clinician may be unable to place each example of the disease in the proper division and 2 any attempt to rely on a histological basis is difficult because as Custer and Bernhard (*1*) have shown the picture may change from one variety to another it may differ from one lymph node to another in the same patient or in different areas of the same node

Until recently following the studies of Custer and Bernhard (*1*) to be discussed later it has been the opinion of many pathologists that there was a constancy over months and years of the reacting cell types and furthermore in routine biopsies it was easy to distinguish between well differentiated lesions It was admitted by some however that with less differentiation it was somewhat more difficult but still possible and in a small number usually estimated at less than 10 per cent with poorly differentiated lesions it became exceedingly difficult In 1942 Gall and Mallory (*2*) studied a group of 618 patients with *malignant lymphoma* and divided them into the following seven varieties The percentage of cases which they found in each group is given as follows

1 Hodgkin s lymphoma	31 2 per cent	
2 Lymphocytic lymphoma	21 9 per cent	
3 Lymphoblastic lymphoma	13 7 per cent	
4 Clasmatocytic lymphoma	11 4 per cent	Reticulum cell sarcoma
5 Stem cell lymphoma	9 1 per cent	
6 Follicular lymphoma	6 6 per cent	
7 Hodgkin s sarcoma	5 8 per cent	

Although the convincing studies of Custer and Bernhard (*1*) demonstrated conclusively the impracticability of placing the disease as it exists

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The types designated as lymphoblastic and lymphocytic lymphoma will be described in the section on lymphatic leukemia Hodgkin s disease and Hodgkin s sarcoma will be presented under the term Hodgkin s disease There remains therefore for consideration the two conditions grouped under the heading of reticulum cell sarcoma which includes both stem cell lymphoma and clasmatocytic lymphoma and the type designated as follicular cell lymphoma

Reticulum Cell Sarcoma —As previously emphasized included in this group by Gall and Mallory (2) are tumors with two types of cells 1 those composed of relatively well differentiated wandering cells with phagocytic ability and 2 those made up of highly undifferentiated presumably pluripotential cells which they have chosen to call stem cells This is by no means a uniform belief but appears to be a helpful classification which can at least be accepted tentatively

The stem cell lymphoma is believed by Gall and Mallory (2) to be made up of undifferentiated cells of mesodermal origin These cells have been termed variously lymphoidocytes primitive blood cells hemohistioblasts reticular or reticulum cells and common lymphoid stem cells The latter term is the one preferred by Gall and Mallory

This cell is large measuring 15 to 35 microns in diameter with variable abundant pale staining amphophilic cytoplasm Although cells of this type may be observed occasionally in all lymphomas they are sometimes the predominant element For this group the name stem cell lymphoma has been proposed (2)

This condition has no distinct clinical picture in my experience Gall and Mallory (2) find that it has its onset at an average age of 42 years that the average duration of the illness is 1 7 years and that 80 per cent of the patients succumb in two years In their series of patients there were 14 per cent of five year survivals and 3 per cent of 10 year survivals Twelve per cent of their cases were radio resistant In about 80 per cent there was involvement of the lymph nodes According to the clinical observations of Gall and Mallory (2) these cases did not appear to differ strikingly from Hodgkin s granuloma except that their course was shorter and they were less amenable to roentgen ray therapy *Such patients in my experience have been regarded as suffering from hemocytoblastoma*

Clasmatocytic Lymphoma —The cells of these tumors according to Gall and Mallory (2) closely simulate normal clasmatocytes or monocytes They are of the opinion that distinction between these two types of cells has been overemphasized They believe that they are closely related and often indistinguishable from each other They found that in patients with this form of lymphoma the average age at the time of onset was 46 years the average duration of the disease 2 1 years and five and 10 year survivals were 11 and 2 per cent respectively Eight per cent of their cases were radio resistant Fever occurred in 25 per cent lymph

in any given patient in a permanent subdivision of classification such a grouping as given above does provide the clinician a working basis for initial therapy *It does not however, furnish an entirely reliable basis for predicting the response to therapy or supplying information of prognostic significance*

Cytologically it is possible to divide the lymphomas into two general groups 1 Hodgkin s disease with its characteristic histologic picture as clearly delineated by Dorothy Reed in 1902 and 2 the simple proliferative disorders of the lymphocytic series of cells variously termed lymphatic leukemia subleukemic leukemia and lymphosarcoma Roulet (3) in 1930 added a third type about which there has been considerable confusion This he called a Retothelsarkom which is usually designated in this country as a reticulum cell sarcoma He included in this term a group of lesions which ranged from one extreme to the other of the malignant lymphomas according to Gall and Mallory (2) It has been regarded variously as a tumor composed of cells less mature than the lymphocyte derived from the germinal centers or the pulp cords (4) as similar to those observed in the embryonic mesenchyme (5) as the same cell as a stem cell (6) as derived from cells of the phagocytic cell series (7) as a cell identical with those in Hodgkin s sarcoma (8) As stated by Gall and Mallory (2) it is apparent that various authorities regard the type cell of this tumor as 1 an immature cell of the lymphocyte series 2 as a cell of variously assumed potentialities of development including the formation of lymphocytes phagocytes reticulum and collagen and 3 as a relatively well differentiated cell of the monocyte or clasmatocyte series These authors conclude that at present the term reticulum cell tumor is an all inclusive one used to designate all primary tumors of lymph nodes not otherwise classifiable They believe that the reticulum cell sarcoma should be divided into two types 1 tumors composed of well differentiated wandering cells with phagocytic ability resembling monocytes or clasmatocytes and 2 tumors made of highly undifferentiated presumably pluripotential cells which they have chosen to call stem cells

Lymphosarcoma —The term lymphosarcoma is not employed by Gall and Mallory (2) as they believe that the condition is merely a transient clinical phase and in most instances might be expected to progress into a generalized process if the patient did not succumb at too early a period They regard this condition as a form of lymphatic leukemia and will not agree that there is a special type of circulating cell which is distinctive of lymphosarcoma In this opinion I do not concur as I believe it is useful at least for the present *to recognize the clinical diagnosis of lymphosarcoma and regard it as an initially circumscribed neoplasm which breaks through its confines and invades neighboring structures through the lymphatics* This is discussed in detail in the section dealing with leukemia

lymphoma In only one case of follicular lymphoma were there leukemic changes in the blood

4 The lymph glands are involved in much the same manner as in Hodgkin s disease as the peripheral nodes were enlarged in 89 per cent the mediastinal in 29 per cent and the retroperitoneal in 63 per cent

In summary it may be said that follicular lymphoma is considered to have a distinctive pathological picture which rarely changes to other types of lymphoma The studies of Custer and Bernhard (*1*) however, show that such a change does occur The onset is later in life the course is longer and the constitutional and visceral manifestations occur less commonly than in other types of lymphoma Furthermore the thera peutic response to roentgen ray is much more satisfactory than in the allied conditions

Hodgkin s Sarcoma —It is probable that a transformation of Hodgkin s granuloma into a sarcomatous process does occur in a certain propor tion of cases and according to Ewing (*4*) as the cells are of an endothelial nature this tumor might be classed as an endothelioma In his opinion they lose their endothelial characteristics and appear as large round cells It is the conclusion of Krumbharr (*11*) that the concept developed by Ewing of the transformation of some cases of Hodgkin s sarcoma into true sarcoma (Hodgkin s Sarcoma") should be generally accepted and it is quite compatible with the modern ideas of cancer genesis He points out however that the large round cells would "in modern parlance be classified as derived from the reticulo-endothelial system Furthermore this author states that it is possible to explain a neoplastic transformation either of the type cell of the lesion or of surrounding tissue cells which have been irritated by the lesion He concludes that such a transformation does not happen commonly for if one would eliminate on the one hand those that still have the granulo matous appearance and on the other hand those for which the granu loma picture was never established histologically he believes that there will not be many cases of Hodgkin s sarcoma left" This view is in accord with that of Gall and Mallory (2) who found in their series that only a few cases exhibited histologic metamorphosis of this type although the clinical histories in many cases suggested that such a change had taken place In their experiences most of the cases of Hodgkin s sarcoma have shown the characteristic morphology of this type from the onset

From my own experience it has been difficult to appreciate that there is a clear cut clinical picture which is characteristic of Hodgkin s sarcoma but perhaps I have not given a sufficient amount of care to delineating such a clinical syndrome In the extensive study of Gall and Mallory (2) it is stated that cases of Hodgkin s disease have been observed in which a relatively benign course both clinically and histologically have been transformed into that of a rapidly progressive highly malignant tumor

node involvement in 80 per cent splenomegaly in 23 per cent anemia in 17 per cent monocytosis in 22 per cent, a leukemic blood picture in 5 per cent *From a standpoint of clinical classification, it has been my custom to include these cases as histio monocytic leukemia*

Follicular Lymphoma—It has been concluded by some (9) that this condition is a form of malignant disease of lymphoid tissue which is a distinct entity with many characteristic clinical and structural features The condition was first described by Brill Baehr, and Rosenthal in 1925 (10) who at first did not consider it to be neoplastic in nature but later revised their opinion By others, it is still considered to be non neoplastic but it is admitted that frequent transitions of the process into a neoplasm do occur Jackson has stated that the condition may be transformed into other forms of malignant lymphoma and Gall and his collaborators have reported that it may be associated with the blood picture of lymphocytic leukemia By some it is considered to be an early form of lymphatic leukemia or lymphosarcoma

The pathological changes in this condition are said to be distinctive and reference should be made to special articles for the details of these *One of the most careful pathological and clinical studies of the condition* is that of Gall, Morrison and Scott (9) In general, it may be said that there is moderate enlargement of the lymph nodes with replacement of the normal architecture with multiple follicle like nodules of varied size Normal sinus structure is obscured and there is frequently an invasion of the capsule There may be an extension of the process of the perinodal tissues where the follicle like type of growth may persist, even beyond the confines of the lymph nodes The process differs sharply from that *observed in other types of malignant lymphoma for it has an apparent* resemblance to the structure of simple lymph node hyperplasia

Certain clinical manifestations are said to be distinctive In the group of cases observed by Gall Morrison, and Scott (9) the following observations were made

1 *It appears much later in life than other lymphomas* the average being 50 years of age 72 per cent of all cases had the first symptoms appear after 40 years of age In only 3 5 per cent was the onset under the age of 20 years

2 The prognosis with regard to the duration of the condition was considerably longer in this group averaging six years as compared to three years in lymphomas of other types

3 Fever is less commonly present as it occurred in only 16 per cent of the group with follicular lymphoma as compared to 40 per cent of other types of lymphoma Furthermore there is less tendency to involve the spleen the bones the gastro intestinal tract the skin, the genito urinary tract the lungs and the mediastinum Anemia occurred in 18 per cent of the patients as compared with 39 per cent in other types of

lymphoma In only one case of follicular lymphoma were there leukemic changes in the blood

4 The lymph glands are involved in much the same manner as in Hodgkin s disease as the peripheral nodes were enlarged in 89 per cent the mediastinal in 29 per cent and the retroperitoneal in 63 per cent

In summary it may be said that follicular lymphoma is considered to have a distinctive pathological picture which rarely changes to other types of lymphoma The studies of Custer and Bernhard (*1*) however show that such a change does occur The onset is later in life the course is longer and the constitutional and visceral manifestations occur less commonly than in other types of lymphoma Furthermore the therapeutic response to roentgen ray is much more satisfactory than in the allied conditions

Hodgkin s Sarcoma —It is probable that a transformation of Hodgkin s granuloma into a sarcomatous process does occur in a certain proportion of cases and according to Ewing (*4*) as the cells are of an endothelial nature this tumor might be classed as an endothelioma In his opinion they lose their endothelial characteristics and appear as large round cells It is the conclusion of Krumbharr (*11*) that the concept developed by Ewing of the transformation of some cases of Hodgkin s sarcoma into true sarcoma ("Hodgkin s Sarcoma") should be generally accepted and it is quite compatible with the modern ideas of cancer genesis He points out however that the large round cells would "in modern parlance" be classified as derived from the reticulo-endothelial system Furthermore this author states that it is possible to explain a neoplastic transformation either of the type cell of the lesion or of surrounding tissue cells which have been irritated by the lesion He concludes that such a transformation does not happen commonly for if one would eliminate on the one hand those that still have the granulomatous appearance and on the other hand those for which the granuloma picture was never established histologically he believes that "there will not be many cases of Hodgkin s sarcoma left" This view is in accord with that of Gall and Mallory (2) who found in their series that only a few cases exhibited histologic metamorphosis of this type although the clinical histories in many cases suggested that such a change had taken place In their experiences most of the cases of Hodgkin s sarcoma have shown the characteristic morphology of this type from the onset

From my own experience it has been difficult to appreciate that there is a clear cut clinical picture which is characteristic of Hodgkin s sarcoma but perhaps I have not given a sufficient amount of care to delineating such a clinical syndrome In the extensive study of Gall and Mallory (2) it is stated that cases of Hodgkin s disease have been observed in which a relatively benign course both clinically and histologically have been transformed into that of a rapidly progressive highly malignant tumor

They note the following differences clinically in this form and the usual Hodgkin's granuloma The onset is at a somewhat older age the average for Hodgkin's disease being 36 whereas in Hodgkin's sarcoma it was 45 years In 61 per cent of the cases of the latter disease, the onset was after 40 years of age, and in only 37 per cent of those with Hodgkin's disease was the onset after this age The total duration in the case of Hodgkin's disease was 4 2 years, and 1 8 years in Hodgkin's sarcoma As would be expected 20 per cent of the latter type of cases were radio resistant, whereas only 8 per cent of the former were in this class Splenomegaly was present in 45 per cent of the cases of Hodgkin's disease and in only 18 per cent of the cases of Hodgkin's sarcoma In both forms of the disease, the lymph nodes were enlarged in about 95 per cent of the cases In Hodgkin's sarcoma involvement of the gastro intestinal the genito urinary and the respiratory tracts and the skin was somewhat greater than in Hodgkin's lymphoma Fever occurred in 59 per cent of their cases of Hodgkin's sarcoma which was about 10 per cent more than in those with Hodgkin's granuloma Jackson (*12*) states that death occurs in a majority of patients with Hodgkin's sarcoma within one year and none are alive over three years On the other hand Slaughter and Craver (*13*) report that in 265 cases of Hodgkin's disease proven by biopsy there were 14 cases of Hodgkin's sarcoma Seven died within one year after the onset of treatment but the others survived respectively 13 months 25 months 50 months five years six years six years and seven and one half years In one of my own most favorable cases, in which there was striking destruction of the cervical vertebrae the diagnosis by biopsy was Hodgkin's sarcoma The patient is now in good health 10 years after the diagnosis was made is working every day and has no complaints except a stiff neck

Classification Suggested by Jackson—The idea that Hodgkin's disease should be divided into the following three main types has been suggested by Henry Jackson (*12*) paragranuloma granuloma and sarcoma It is his opinion that the pathologic picture the clinical aspects and the prognosis differ materially in the three forms The basis for this grouping is as follows 1 That in each there must be the so called Reed Sternberg cells as the diagnosis cannot be made in their absence and 2 eventually there may be a transformation of one type of the disease into another For example it is his opinion that a patient may first have a Hodgkin's paragranuloma and months or even years later it may be transformed into a Hodgkin's granuloma Similarly he contends that a granuloma may become a sarcoma or much more rarely the two forms may be found co existing in the same patient or even in the same node What is regarded as the more benign forms (paragranuloma and granuloma) may progress into the more malignant one such as Hodgkin's sarcoma but never does the reverse occur

More specifically Jackson and Parker (*14*) define the three types of Hodgkin's disease as follows

1 Hodgkin's *paragranuloma* Patients with this type may live for years unless the condition undergoes a change to the more rapidly advancing granulomatous type It bears little relation to a true tumor either in its histologic picture or its clinical course These authors consider that the benign course the complete lack of invasiveness the fact that the condition usually starts in the neck where the causative agent may have gained entry through the pharynx all bespeak to them in favor of an infectious process

2 Hodgkin's *granuloma* This is the familiar type about which there is still controversy as to its cause the beliefs being among different authoritative workers that it is 1 a neoplasm 2 an infectious process or 3 a combination of the two

3 Hodgkin's *sarcoma* It is their opinion that this condition has all of the characteristics of a true neoplasm This is based on the uniformity of the cellular constituents the aggressive invasive nature of the process the extremely short duration of life and the not uncommon finding of a large destructive tumor with comparatively free metastases all of which favor this concept This view is contrary to that of others who contend that the cellular type is merely a variant of the granulomatous form and has its basic structure Jackson and Parker (*14*) believe that they have observed sarcomatous transformation in certain cases of Hodgkin's disease and Ewing (*4*) speaks of the same alteration

Interrelation between Hodgkin's Disease and the Other Lymphatic Tumors —As stated above Custer and Bernhard (*1*) after studying the interrelationship between Hodgkin's disease and other lymphatic tumors have concluded that the cellular structure of such tumors is extremely labile and transitions from one distinct type to another occurs frequently The predominating cell pattern at any one examination may indicate either one of the three forms of Hodgkin's disease (paragranuloma granuloma or sarcoma) follicular lymphoblastoma lymphosarcoma reticulum cell sarcoma lymphatic leukemia or monocytic leukemia *They believe that these terms are useful only to designate the predominating histologic pattern of a lymphoma at any one particular time A rigid classification of lymphatic tumors therefore is not warranted The entire group in their opinion may be regarded as a single neoplastic entity having a number of variants*

A corroborating opinion has recently been expressed by Videbaek (*15*) After studying a group of 312 patients to determine whether the usual classification of malignant lymphomas based on histological changes is also applicable to the clinical findings or whether the basis is purely morphological he says "Instead of losing oneself in the study

They note the following differences clinically in this form and the usual Hodgkin's granuloma. The onset is at a somewhat older age, the average for Hodgkin's disease being 36, whereas in Hodgkin's sarcoma it was 45 years. In 61 per cent of the cases of the latter disease the onset was after 40 years of age and in only 37 per cent of those with Hodgkin's disease was the onset after this age. The total duration in the case of Hodgkin's disease was 4.2 years and 1.8 years in Hodgkin's sarcoma. As would be expected, 20 per cent of the latter type of cases were radio-resistant whereas only [illegible] per cent of the former were in this class. Splenomegaly was present in 45 per cent of the cases of Hodgkin's disease and in only 18 per cent of the cases of Hodgkin's sarcoma. In both forms of the disease the lymph nodes were enlarged in about 95 per cent of the cases. In Hodgkin's sarcoma involvement of the gastro-intestinal, the genito-urinary, and the respiratory tracts and the skin was somewhat greater than in Hodgkin's lymphoma. Fever occurred in 59 per cent of their cases of Hodgkin's sarcoma which was about 10 per cent more than in those with Hodgkin's granuloma. Jackson (*12*) states that death occurs in a majority of patients with Hodgkin's sarcoma within one year and none are alive over three years. On the other hand, Slaughter and Craver (*13*) report that in 265 cases of Hodgkin's disease proven by biopsy there were 14 cases of Hodgkin's sarcoma. Seven died within one year after the onset of treatment but the others survived respectively 13 months, 25 months, 50 months, five years, six years, six years, and seven and one half years. In one of my own most favorable cases in which there was striking destruction of the cervical vertebrae the diagnosis by biopsy was Hodgkin's sarcoma. The patient is now in good health 10 years after the diagnosis was made, is working every day, and has no complaints except a stiff neck.

Classification Suggested by Jackson.—The idea that Hodgkin's disease should be divided into the following three main types has been suggested by Henry Jackson (*12*): paragranuloma, granuloma, and sarcoma. It is his opinion that the pathologic picture, the clinical aspects and the prognosis differ materially in the three forms. The basis for this grouping is as follows: 1. That in each there must be the so-called Reed-Sternberg cells as the diagnosis cannot be made in their absence and 2, eventually there may be a transformation of one type of the disease into another. For example, it is his opinion that a patient may first have a Hodgkin's paragranuloma and months or even years later it may be transformed into a Hodgkin's granuloma. Similarly he contends that a granuloma may become a sarcoma or, much more rarely, the two forms may be found co-existing in the same patient or even in the same node. What is regarded as the more benign forms (paragranuloma and granuloma) may progress into the more malignant one such as Hodgkin's sarcoma but never does the reverse occur.

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of structural differences, sometimes approaching morphological hair splitting and in more or less strained attempts at differentiating special groups of diseases on that basis, it would seem reasonable to *collect these malignant lymphomas under one heading* and regard the types not as different tumors, successfully trying to give each its clinical features but *interpret them simply as more or less differentiated types of the same growth* (malignant lymphoma)

Although this view has been advocated previously, the unprecedented opportunity afforded Custer and Bernhard of multiple biopsies on the same patients and frequently examination of necropsy material in untreated Army cases in World War II made available concrete and convincing evidence, hitherto unavailable in support of this conclusion

Terms which have been employed to designate the cellular pattern of a lymphoma at any given time are as follows

1 *Hodgkins granuloma paragranuloma* and *sarcoma* (defined under Hodgkins disease page 895)

2 *Follicular lymphoma* a lymphatic tumor, localized or multi centric in which there is differentiation into follicles

3 *Lymphosarcoma* a tumor consisting of relatively uniform round cells which may be small well differentiated lymphocytes or large immature lymphocytes

4 *Reticulum cell sarcoma* is made up of very large cells with big nuclei This type has been designated by some as stem cell lymphoma clasmatocytic lymphoma and other terms to indicate the highly undifferentiated form of the cells observed in this disease

5 *Mycosis fungoides*—This condition is now generally regarded as a neoplasm with tumor like changes in the skin and ultimate histologic evidence of involvement of the superficial and deep lymph nodes the bone marrow and other tissues with Hodgkins disease lymphosarcoma or lymphatic leukemia The form usually encountered develops following a premycotic lesion characterized by a desquamative dermatitis with pruritus which may in some instances precede the formation of cutaneous tumors for years but in some patients the tumors may be the initial evidence of a lymphoma The tumors are raised purplish red areas of infiltration which usually exceed three cubic centimeters in diameter Ulceration occurs late in the disease

HODGKINS LYMPHOMA

Synonyms —Malignant lymphoma, Hodgkins granulomatous lymphoma chronic benign lymphomatosis lymphoblastoma of the Hodgkins type, scirrhous lymphoblastoma These are only a few of the more common names which have been given to the disease As Wallhauser (*16*) says Perhaps no other disease has been encumbered with a more suprising array of names than has Hodgkins disease He lists over 60 synonyms

which have been employed by various authors It is suggested by Krumbhaar (*17*) that the eponymic term Hodgkin s disease in view of its priority long usage and desirable indefiniteness should be used as was done universally for some 30 years at least until its true nature is established It is to be commended that there is a distinct tendency in this country to return to this custom

History —The earliest reference to a condition which can be recognized as possibly Hodgkin s disease is that made by Malpighi (*18*) whose work on the structure of the liver kidneys and spleen did much to advance the physiologic knowledge concerning these organs This famous observer commented on a fatal condition associated with general enlargement of the lymph glands and the spleen as follows They (granules in the spleen of animals) are less evident in man if however the entire glands of the neck swell from the disease they (the granules) become more noticeable since their size increases such as I have observed in a dead girl whose entire spleen revealed conspicuous globules scattered about like clusters of grapes This statement was called to the attention of Hodgkin by G O Heming and is included as a footnote in Latin by Hodgkin in his original communication published in 1832

It was Thomas Hodgkin the devout member of the Society of Friends and curator of the pathological museum and demonstrator of anatomy of Guy s Hospital who first gave special attention to the subject in a paper entitled Some Morbid Appearances of the Absorbent Glands and Spleen (*19*) In the first sentence of the paper Hodgkin modestly asserts that what he was going to say was probably familiar to many practical morbid anatomists but these findings have not been the subject of special attention This was probably true and somewhat difficult to explain as undoubtedly pathologists previously had noted enlargements of the spleen and lymph glands but no attempt had been made to group such cases into a pathologic syndrome until the report of Hodgkin Occasionally cases were reported but it is difficult to differentiate them from tuberculosis and leukemia One such example is given by Morgagni (*20*) The case was that of a boy age 15 who observed the enlargement of the glands of the neck The glands beneath the jaw in the neck and thorax were all enlarged and tumors of the same character existed in the integuments of the abdomen and in the abdominal cavity The progress of the disease was rapid and accompanied by fever

Information concerning seven cases was recorded in detail by Hodgkin who gave the principal findings as lymphadenopathy and splenomegaly The author states that this enlargement of the glands appeared to be a primitive affection of these bodies rather than an irritation propagated from some ulcerative surface A few paragraphs later he states that the spleen with one exception had been found more or less diseased and in some thickly pervaded with defined bodies of various

sizes in structure resembling that of the diseased glands He concludes that there be a close connection between the derangement of the glands and that of the spleen

A careful scrutiny of the data concerning the seven cases presented by Hodgkin indicates to Fox (*21*) that three and possibly four of them only were true examples of what we would now consider to be the disease It is of interest that in a copy of the original communication of Hodgkin presented to the Welch Library of the Johns Hopkins Hospital and Medical School by the late William Stewart Halstead Professor of Surgery at that institution contains notes apparently by this great surgeon (*22*) which indicates that his idea of the diagnosis in the seven cases was as follows Case No 1 tuberculosis (?) Case No 2 probably Hodgkins *No 3 tuberculosis No 4 Hodgkins No 5 Hodgkins No 6* not annotated No 7 sarcoma (?) As Jones (*22*) says concerning the diagnosis of Halstead Three cases then of true Hodgkins disease but the excellent example according to Hodgkin himself of Case No 7 was diagnosed sarcoma

In the past the significance of Hodgkins contribution has been minimized chiefly because several types of glandular enlargement due to different causes were included in the group It must be admitted however that he did direct attention to an important group of cases which had previously been ignored as a possible disease entity

His contribution did not however appear to arouse much interest until *1856 (23)* when Samuel Wilks independently observed similar cases which he reported under the title of Cases of Lardaceous Disease and Some Allied Affections With Remarks In this paper a condition characterized by enlarged lymph glands and an abnormality of the spleen was described but at that time he apparently was not familiar with the prior contribution of Hodgkin This he acknowledges graciously in his second publication in 1865 (*24*) with the statement that Although my observations were at the time original I have been forestalled by Dr Hodgkin who was the first as far as I am aware to call attention to this peculiar form of disease In 1865 Wilks published a second paper on the subject entitled Cases of Enlargement of the Lymphatic Glands and Spleen (or Hodgkins Disease) with Remarks In this group he includes four of the seven cases observed by Hodgkin in his paper published 32 years before and added 12 more collected from the literature and his own experience He summarizes his views concerning this condition by the statement that it is characterized by an enlargement of the spleen and lymph glands and that it may be accompanied by anasarca and a striking anemia It was his opinion that such a change was due to a malignant condition which must take its place amongst those affections which are characterized by development of new growths in the system He recognized that the lymphatic glands usually became

enlarged before the system suffers and that then the spleen becomes involved and afterwards the other organs

In addition to the above Wilks makes another important and original observation namely that he had failed to find an excess of white corpuscles in the blood except in two of the cases In both of these the red and white corpuscles appeared to be about in equal proportions In other words in these two instances he was undoubtedly dealing with a chronic leukemia probably lymphatic in nature To Wilks must be accorded the credit for recognizing the malady as a distinct and separate clinical entity and in 1856 labeling the condition Hodgkin s disease It was not until 1858 that Wunderlich (25) attempted to separate Hodgkin s disease from subleukemic leukemia In 1890 Waetzoldt (26) clarified the situation by showing that tuberculosis was a frequent terminal complication of Hodgkin s disease

Many other names were applied to the disease especially in Germany and also in France The name progressive multiple gland hypertrophy was used in 1856 by Wunderlich lymphosarcoma in 1864 by Virchow (27) pseudoleukemia by Cohnheim (28) in 1865 adenie by Trosseau in 1865 (29) multiple lymphadenoma without leukemia also by Wunderlich in 1866 (30) malignant lymphoma by Billroth (31) in 1869 In more recent years Benda (32) added the name malignant granuloma Lymphogranuloma was introduced by Gross (33) in 1906 and scirrhous lymphoblastoma by Mallory (34) in 1914 The name Hodgkin s disease was employed by the *Index Medicus* whereas the *Quarterly Cumulative Index* used the term lymphogranuloma until 1941 when Hodgkin s disease was again introduced

The large number of names given to the disease is listed along with the appropriate references for two main reasons first it gives some idea concerning the interest in the disease by clinicians and pathologists of standing in various countries Furthermore it is probably true that the multiple terminology of any condition is a good indication that its underlying nature is probably unknown

For several years following the description of the disease by Wilks (24) in 1865 the knowledge concerning it could be summarized completely as follows It was considered to be a disorder characterized by either hard or soft tumors of the lymph glands splenomegaly anemia without leukocytosis fever and a fatal cachexia The only histological information concerning the condition were changes considered to be simple hyperplasia of some or all of the lymph glands and areas or nodules of such tissue in the internal organs From an etiological standpoint it was considered by some to be a true neoplasm by others an infectious process and still others some type of constitutional disturbance

A considerable advance in our knowledge of the disease but one which did not receive widespread recognition was made in 1878 by

Greenfield (35) He described with remarkable accuracy, the gross and microscopic changes in the glands and first brought to the attention of the pathologists the fact that there was an increase of fibrous tissue in the glands and also multinuclear giant cells Furthermore, he definitely differentiated such cases from leukemia, and noted that clinically the disease is characterized by an irregular febrile course, periods of latency and progression and a severe anemia It was Goldmann (36) in 1892 who added the significant observation that eosinophils were often present in the diseased tissues

According to Longcope (37) Virchow (38) in 1864 and Langhans (39) in 1872 speak distinctively of the uninuclear and multinuclear giant cells and several authors had noted the reticular thickening as well as the coarse connective tissue growth. In 1898 Sternberg (40, 41) collected the cases of pseudoleukemia associated with tuberculosis and added to them some of his own cases in which tubercle bacilli were either present or the tissue changes were suggestive of the disease His views had great influence on the claim that Hodgkin s disease was in reality a peculiar form of lymphatic tuberculosis It remained for Dorothy Reed in 1902 (42) Simmons (43), and Longcope (37) to evaluate all of the former contributions add their own and place our knowledge of the condition on a firm foundation by the correlation of the clinical pathological data

The observations of Reed (42) made in 1902 are of special value She concluded that Hodgkin s disease is a clinical and pathological entity characterized by painless progressive glandular enlargements usually starting in the neck without the blood changes of leukemia that the histologic picture is specific and that tuberculosis has no relation to the subject She (42) makes the following statement which is responsible for the clear delineation of the pathological condition in modern times We believe then from the description in the literature and the findings in eight cases examined that Hodgkin s disease has a peculiar and typical histological picture consisting of proliferations of the endothelial and reticular cells formations of lymphoid cells and characteristic giant cells and a gradual increase of connective tissue resulting in fibrosis and in most of the specimens in the presence of a great number of eosinophils

The credit for having recognized the ever present and diagnostic giant cells is a matter of personal choice in the opinion of Jackson and Parker (14) These students of the disease make the following statement These cells were recognized by Greenfield in 1878 and their characteristics fully depicted by Sternberg in 1898 but Sternberg had the misfortune to study a series of cases of Hodgkin s disease combined with active tuberculosis, and only in his late years did he give up the idea that he was dealing with a peculiar form of tuberculosis Perhaps the greatest credit should

go to Reed who described the cells even more accurately than did Sternberg and who recognized clearly that they were an integral part of the disease described by Hodgkin seventy years before"

In a scholarly review of the development of our knowledge of the histology of Hodgkin's disease and its characteristic cells Jones (22) formulates the following conclusions concerning which one of the investigators is entitled to the eponymic honor As Sternberg not only did not first describe the characteristic cells but failed to assign them a place in the histological picture of Hodgkin's disease (considering them rather a peculiar form of tuberculosis lymphadenopathy) he deserves little or no consideration except for the fortuitous circumstance of having appended excellent illustrations Those who should receive credit are Langhans (39) Dietrich (44) Fischer (45) and Reed (42) The contribution by Greenfield in 1878 is completely disregarded For various reasons which Jones gives in his original article he concludes that The process of elimination leaves Dorothy Reed as the remaining one to whom eponymic honors might be accorded her conclusions formulated years ago are true today without revision

An excellent group of articles dealing with Hodgkin's disease its historical aspects pathology and the symptoms and course have been written recently by Jackson and Parker (*14 45a 46*) and by Hoster and *his associates* (*47*)

Earliest Use of the Roentgen Ray.—The roentgen rays were first employed in the treatment of Hodgkin's disease by William Allen Pusey in 1901 and reported in the literature the following year (48 49) The first patient treated was a boy four years of age in whom the biopsy report had been "pseudoleukemia but in whom the clinical diagnosis of Hodgkin's disease had been made There were glands on the right side of the neck about the size of a small fist and a small swelling on the left side about one half the size of those on the right The patient was first treated with exposure to x rays on September 11 1901 by Dr Pusey There was prompt regression in the size of the neck glands and general improvement in the condition of the patient The glands recurred within a relatively short time thereafter and death followed their operative removal Other early reports of the use of the roentgen rays in the treatment of this condition were those of Hett (50) Williams (51) Dunn (52) Rodman and Pfahler (53) Butler (54) and Childs (55) It is concluded by Pusey and Caldwell (56) in 1904 that most of these reports were too early to warrant any opinion as to the permanent result of the treatment but they indicated clearly the beneficial effects of the x ray in such cases Further it appeared that by the use of the x ray years of usefulness may be added to the lives of these patients by the long continued application of this agent

In a letter written by William Allen Pusey in the *Journal of the American Medical Association* in 1904 (57) he states that Nicholas Senn has

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which the temperature is normal or nearly so He displays on page 548 a typical febrile curve of which is now designated as the Pel Ebstein fever This form of temperature curve which occurs in about one sixth of the cases of Hodgkin s disease was described also in 1885 by Pel (66) and by Ebstein in 1887 (67) The latter author assigned a new name to this febrile condition "Chronic relapsing fever" as he did not want to include such cases with pseudoleukemia

History of Development of Our Knowledge Concerning the Skin Lesions in Hodgkin s Disease—In his admirable article on Hodgkin s disease in Reynolds *System of Medicine* published in 1880 Gowers makes but slight reference to the skin lesions in this condition His comments that in addition to pallor there may be "bronzing of the skin and that certain skin diseases are not uncommon during the cachectic period especially a papular rash on the backs of the forearms and hands furuncles and pemphigus" Osler (68) in his article in *The System of Medicine* edited by Pepper published in the year 1885 says with reference to the condition of the skin that the skin may be the seat of adenoid growths The growing tumors may involve it and ulceration may occur" It is of interest that neither Gowers nor Osler both being astute observers with an extensive clinical experience makes mention of pruritis as a complaint in these patients

One of the earliest references to the occurrence of skin manifestations in Hodgkin s disease is contained in the case report of Hutchinson (69) in 1875 in which he records that his patient had "numerous tumors varying in size from a millet seed to a walnut for the most part situated beneath the skin " It is of interest to note that in this same medical periodical appearing just one week before the article by Hutchinson there is a letter from Kaposi (70) protesting that the condition which he had described as "Lymphangioma cutis" had been referred to as Hodgkin s disease and that he wished to correct this error He also stated at this time that in Hodgkin s disease the skin lesions are subcutaneous nodes composed of hyperplastic subcutaneous lymphatic glands

The exact place of mycosis fungoides historically is difficult to determine as is its relation to Hodgkin s disease at the present time Apparently the first description of the disorder was in 1814 by Alibert (71) who described it as "Pian Fongoides In 1885 Tilden (72) states with regard to mycosis fungoides as follows With regard to the affection being leukemia or pseudoleukemia in nature so little is known as to the true nature of leukemia and pseudoleukemia that speculation as to their possible relationship with mycosis fungoide is rather barren in only two autopsies has there been found enlargement of the spleen an enlargement which together with that of the lymphatic glands is an essential feature in pseudoleukemia"

been given the credit for first having treated cases of pseudoleukemia with the roentgen rays as the result of the publication of his article in the *Medical Record* for August 22 1903 (58) In this paper he does not make reference to previous articles dealing with x ray treatment of either pseudoleukemia or leukemia Among other prior references Pusey cites correctly his own work as being the first to appear He refers to his two articles dealing with the subject which were published in the *Journal of the American Medical Association* for April 12 1902 and June 18 1902 Furthermore he states that his first cases of pseudoleukemia treated with the roentgen rays were demonstrated before the Chicago Medical Society of February 26 1902

It was in 1871 that Billroth (59) first mentioned arsenic in the treatment of Hodgkin s disease

Changes in the Bones—According to Steiner (*60*) the osseous lesion in lymphogranulomatosis were first described by Benda (*61*) although he states that changes which were possibly examples of the disease had previously been presented by Hammer (*62*) and others It is emphasized by Steiner, quite correctly that the uncertainty in regard to the early cases arises from the fact that a clear histological picture of the disease was not made until 1898 by Sternberg and 1902 by Reed As early as 1861 Perrin (*63*) reports a case in which the ribs could be cut through with a scalpel and the least pressure caused their fracture Gowers (*64*) writing in 1880 states that under the microscope the altered medulla presents abundant lymphoid cells and rather larger cells with very large nucleolated nuclei Thus there is a substitution of adenoid tissue for the normal elements of the medulla

Fever in Hodgkin s Disease—It is of interest to note that Hodgkin refers in his original communication to one of the patients Martha Newton as labouring under intermittent fever but her appearance did not altogether accord with the idea of ague It is reported that she had two paroxysms after admission to the hospital which were not relieved by quinine This could well have been the intermittent type of fever which later became known as the Pel Ebstein variety characteristic of a certain proportion of cases of Hodgkin s disease In 1870 Charles Murchison (*65*) reports the case of a patient with Hodgkin s disease who had febrile attacks and states that of the recorded cases in one so far as I have been able to discover have there been noted paroxysms of fever marking the periods of growth of the enlarged glands Gowers (*64*) in his article on Hodgkin s disease in Reynolds *System of Medicine* published in 1880 states that fever occasional or constant is a frequent but not invariable symptom of the disease He comments on a second type of fever characterized by periods of pyrexia in which for several days a high temperature is maintained the daily variation being slight Alternating with these pyrexial periods are intervals of several days in

the ovary protects the individual to a certain extent and when the disease does appear in the female it is associated with hypofunction of this endocrine gland

It is well recognized that Hodgkin s disease may occur at any age but its greatest incidence is claimed by some to be in the third decade In a group of 759 cases tabulated by the New York City Department of Health from 1940 to 1944 Hoster (77) found that the curve for males reached a peak in the 45 to 49 age group and in females in the 25 to 29 age group The literature is cited by Hoster (47) to the effect that a child may be born with the disease and four cases have been reported as occurring in infants between the ages of two and five months According to Hoster (47) cases have been observed in the ninth and even tenth decade The youngest case in Goldman s series (78) was six years and the oldest 76 years There is some evidence to indicate that the disease is more prevalent in children in the first five years of life and that relatively few cases are present at the time of puberty

It is stated by Jackson and Parker (46) however that a study of the literature indicates that no age is spared and that the condition is found with reasonable constancy throughout the first seven decades of life Their own experience indicates that the cases are distributed from earliest childhood to the age of 70 years It is their opinion that Hodgkin s sarcoma occurs chiefly in the middle aged or elderly Eighty per cent who were regarded as having this type of the disease were over 40 years of age In no case have they observed a patient with primary Hodgkin s sarcoma—that is not preceded by Hodgkin s granuloma—under 20 years of age

The Nature of Hodgkin s Disease —Opinion is divided among workers in this field concerning the nature of Hodgkin s disease The theories offered may be divided into three groups namely 1 it is an infection possibly due to an atypical tubercle organism to a virus or other organisms 2 it is neoplastic in nature and 3 its origin is totally unknown A most comprehensive discussion of the nature of Hodgkin s disease with a review of the literature is given by Hoster and his collaborators (47)

Of all the organisms which have been suggested as a cause of the condition there are only two at present which deserve consideration One is the tubercle bacillus which for years has been considered as possibly related to the etiology of the disease and the other the brucella group of organisms Undoubtedly tuberculosis and Hodgkin s disease co exist frequently in the same person but this does not prove a causal relationship Ewing s apt and oft quoted phrase that tuberculosis follows Hodgkin s disease like a shadow has often been evoked to emphasize the close association between the two conditions For many years this relationship between Hodgkin s disease and tuberculosis has been noted

The literature concerning the skin involvement in Hodgkin's disease is available in articles by Pinkus (73) Alexander (74) and Schoenhof (75)

Frequency, Sex and Age Incidence —It is difficult to estimate accurately the exact incidence of Hodgkin's disease Often the diagnosis of the condition has been made without microscopic examination of tissue from the patient, either by biopsy or at necropsy In more recent years however there is a desirable effort made to obtain biopsies on all patients suspected of having the malady Basing his report on tissue from necropsies or biopsies, which he examined himself Uddstromer (76) estimates an incidence of 0 054 case per 10 000 living persons It is reported by Wallhauser (16) that when combined necropsies numbering 15 783 cases of disease in general are considered it was found that 38 had Hodgkin's disease or an incidence of 0 24 per cent This compares very closely with the estimate that Hodgkin's disease makes up 0 25 per cent of all deaths at a general hospital (14) At the Memorial Hospital in New York City, these patients comprise 1 75 per cent of all admissions but it should be remembered that in this institution there is a very extensive service for the treatment of tumors

An extensive study of this question has been made by Hoster (77) who records that the incidence in the United States varies from 0 5 to 2 5 per 100 000 living population This same observer and his associates (47) estimate that the condition accounted for 1 9 average deaths per 100 000 living persons in New York City (1931–1944)

In general it can be said that the average incidence in relation to all diseased conditions is a great deal less than 1 per cent This seems a low estimate judging from my own experience but it may be explained by the fact that I have always been associated with institutions since graduation from medical school in which there has been a special interest in diseases of this nature Furthermore one is likely to gain false ideas of the frequency of any chronic disease which is benefited but not cured by the use of the roentgen ray This is because the patient is likely to have multiple admissions and in many instances the stay in the hospital is of relatively long duration

The predominance of the disease in the male sex is well established by statistics from various areas of the United States and other countries Wallhauser (16) quotes the combined figures from 21 publications in which 1447 patients are considered Of these 1009 were males and 438 females which gives a ratio of males to females of 2 3 to 1 This proportion appears to be well established and is the one now generally accepted According to Hoster (47) males are affected almost twice as commonly as females and in children the ratio increases to more than 4 1 There has been considerable speculation as to why the disease is less prevalent in the female One theory which is purely speculative is that

The *neoplastic theory* which has been sponsored in this country by Mallory and Warthin has as its chief support the fact that the condition is widespread in the body and the lesions are infiltrative in character Furthermore evidence in favor of this idea is the fact that the disease has a 100 per cent mortality While this is suggestive it is not conclusive Moreover the histologic picture of the disease process does not resemble any known neoplasm but more closely simulates a chronic inflammatory reaction The observation of Ewing and others that some cases undergo a transformation into a true sarcoma is undoubtedly correct but this may be interpreted as due to a neoplastic transformation of the cell type of the lesion or of the surrounding cells which have been irritated by the original pathological process It is not convincing evidence for or against the neoplastic theory of the primary disease From the study of tissue cultures obtained from the glands of untreated patients with Hodgkin s disease it appears that the cells grow and stain more like inflammatory cells than those of a neoplastic nature

In my own experience from a purely clinical standpoint it seems more helpful to consider the disease neoplastic in nature because of its inevitable fatal termination although of course I realize that this does not necessarily define the term neoplasm Krumbhaar concludes his statement in regard to the etiology of the condition with these carefully chosen words the more provocative view that it is probably due to an infection of unknown nature would seem more likely to foster progress than the hypothesis that it is a malignant neoplasm

After a discussion of the etiology of the disease Jackson makes the following statement in 1939 (*86*) For the present the cause of malignant lymphoma in all its varied forms remains obscure

Pathology—The histologic changes of the condition are usually described as a progressive diffuse process beginning with a lymphoid hyperplasia of the lymph nodes a gradual loss of the normal architecture as a result of its replacement by a polycellular tissue and a terminal picture characterized by the formation of hyaline fibrous tissue

The microscopic changes in the nodes of an average case are highly characteristic and unmistakable The typical findings are a reticulum in which are observed a few small lymphocytes large lymphocytes plasma cells eosinophils proliferating endothelium and endothelial giant cells Although lymphocytes may be present in the early stages these later disappear and are replaced by other cells The follicles and sinuses are obliterated early in the process

Mononuclear and multinuclear giant cells (Sternberg Dorothy Reed cells) are pathognomonic for the condition and their presence is essential for the diagnosis They are not found ordinarily in inflammatory conditions of established etiology although as Jackson and Parker (*46*) state in the cellular reaction to bacillus mallei a characteristic type of

but there has been a difference of opinion concerning the explanation of this Some have thought that the tubercle bacillus played an etiologic role in the causation of Hodgkin s disease, whereas others considered the organism to be merely a secondary invader The results of a study by Parker and his associates (79) have been of importance in this connection They found that tuberculosis occurred in 33 3 per cent of their cases of Hodgkin s disease which is in accord with an incidence of 38 5 per cent reported in the literature The findings by this group of observers appear to be significant because they noted that tuberculosis was present in other types of lymphoma in 5 3 per cent of the cases in cancer in 14 6 per cent and in general necropsies in 19 3 per cent Of even greater interest is the incidence of active tuberculosis in these various conditions This was present in 20 per cent of the cases of Hodgkin s disease in no cases of other types of lymphoma or pernicious anemia in 5 7 per cent of the cases of cancer and in 11 per cent of the general necropsies Their conclusion with which a great majority of present day students of the disease agree is that the frequent association indicates merely that the one predisposes to the other or that the same constitutional type is subject to both They have no explanation for the extremely low occurrence of tuberculosis in other forms of lymphoma but make the suggestion that it may lie in the presence throughout the body of very large numbers of lymphocytes which are well known antagonists of the tubercle bacillus

Recently Hoster Doan and Schumacher (80) have studied the relationship of the tubercle bacillus to Hodgkin s syndrome They report their results after innoculating into animals fresh macerated lymph node and splenic tissue emulsions obtained surgically from patients with Hodgkin s disease In no instance were they able to isolate tubercle bacilli except in histologically bacteriologically and clinically proved cases of tuberculosis From their results it was not possible to conclude that avian bovine or human tubercle bacilli has an etiologic role in Hodgkin s disease Although it is recognized that tuberculosis does exist in some patients with Hodgkin s disease it is their opinion that this evidence does not establish a causal relationship between the two diseases

The literature on the relationship of tuberculosis to Hodgkin s disease is extensive Reviews dealing with this aspect of the disease are those of Wallhauser (16) Sternberg (61), Terplan and Mittelbach (82) and Simonds (83) and Hoster et al (47)

In 1939 Parsons and Poston (84) reported that they had isolated the Brucella organism in some cases of Hodgkin s disease In referring to this work Krumbhaar (11) expressed the fear that it will prove to be only one more in the long list of pseudo causes of the malady In 1944 Hoster Doan and Schomacher (85) reported that an unsuccessful attempt had been made to isolate organisms of the Brucella group from 35 patients with Hodgkin s disease and hence could not confirm findings of these investigators

They are the osseous system the gastrointestinal tract and the mediastinum and lungs

Bone is involved in at least 10 to 20 per cent of the patients A careful search for osseous lesions in each patient would undoubtedly reveal a higher incidence These lesions usually develop late in the course of the disease but they may occur early and in fact be the initial clinical manifestation of the process in rare instances Although attention is usually attracted to the osseous lesions by pain or deformity in some instances they may be painless and are discovered only by routine roentgen ray examination

Hodgkin s disease affects the gastro intestinal tract in almost 25 per cent of the cases (88) The lesions are most frequently observed in the stomach duodenum or small intestine and less commonly in the colon or rectum The areas involved are usually multiple and hence not ordinarily amenable to surgery

Mediastinal involvement is a common and a well recognized part of the disease It is not usually appreciated however that the lungs may show a diffuse parenchymatous infiltration due to Hodgkin s disease which may simulate closely a chronic non suppurative pulmonary lesion

Hodgkin s Sarcoma —According to Ewing (4) the transformation of a Hodgkin s granuloma into a sarcomatous process occurs in a certain proportion of cases Such a condition may be confused with a true lymphosarcoma The new neoplastic cells of a Hodgkin s sarcoma are derived from endothelial cells and appear as large round structures The general structure of a gland with such an involvement varies from one which closely resembles that of true Hodgkin s disease to one composed of tissue which is made up entirely of large round cells These have a faintly staining granular cytoplasm and a moderately chromatic nuclei Large round giant cells with multiple or multilobed nuclei may predominate It has never been demonstrated that true lymphosarcoma in which the cells are neoplastic lymphocytes has ever occurred in Hodgkin s disease

The histologic signs of malignancy are not marked in Hodgkin s sarcoma as the perforation of the capsules of the lymph glands is slow The tendency to fibrosis is pronounced Metastatic tumors are found in the lungs and the liver and less frequently in the nervous system Ewing (4) states that clinical data is inadequate in this field and that microscopic evidence of complete predominance of one atypical cell type and usually the presence of metastases is necessary before the diagnosis of Hodgkin s sarcoma is made

Symptoms and Signs of Hodgkin s Lymphoma —In almost 80 per cent of the cases the onset is with a painless non tender enlargement of a superficial lymph gland This most commonly occurs in the neck and is frequently unilateral although glands on both sides may be noticed at

giant cell is seen Eosinophils are usually numerous but occasionally may be absent A few plasma cells are constantly present Necrosis is not characteristic of the disease process but it may be present in the acute febrile cases and in some patients with extensive glandular enlargement Fibrosis finally becomes established in advanced lesions

A characteristic feature is the local invasive and destructive tendency of the lesions Although the capsule of the glands usually remains unbroken for a long period the surrounding tissue may become invaded by the granulomatous process It may involve the walls of the blood vessels with resultant occlusion of the lumina

Although the changes in the lymph glands have a tendency to follow trends there is no constant chronological sequence It should be emphasized that the disease process does not follow a simultaneously parallel course in every node in any given patient for early lesions may be observed in one area and at the same time the process be advanced in others

It should be emphasized that almost any part of the body may be involved by this pathologic process either grossly or microscopically This tendency toward widespread distribution is the basis for the diversity of symptoms and signs which may arise in this disease

Lymph nodes	59
Spleen	44
Liver	31
Bones	27
Lung	24
Pleura	10
Gastro intestinal tract	10
Peritoneum	10
Kidneys	8
Pancreas	[illegible]
Adrenal glands	8
Diaphragm	7
Uterus	[illegible]
Breast	[illegible]
Skin	2
Thyroid gland trachea aorta ovary bladder	1 each

Organs found to be involved at necropsy in 59 cases of Hodgkin s granuloma (Modified from Jackson and Parker (87))

The table above indicates the frequency of involvement of different parts of the body Except in rare instances, the lymph nodes are enlarged either in the cervical axillary mediastinal maxillary or inguinal regions Evidence of the disease is usually observed in the spleen and liver and in decreasing frequency in the order named the pancreas gastro intestinal tract, bone skin lung heart nasopharynx breasts ovaries and testicles Occasionally involvement of the central nervous system may occur

There are three systems of the body in addition to the lymphatic which may be involved in the pathologic process and deserve special mention

finally developed a small gland just below the clavicle which showed the characteristic histologic changes of Hodgkin's disease. The epitrochlear glands are not commonly involved which is a point to be remembered in the differential diagnosis of lymphosarcoma in which enlargement is relatively common.

In a small percentage of patients some other symptoms may be present before the enlarged lymph glands appear. These are loss of weight, weakness, cough, dyspnea, pruritis, fever, pain in the chest, back, scrotum, hip or sternum, and jaundice. In almost 10 per cent of the patients the earliest manifestations of the disease are weakness and loss of weight. Of special interest is the onset with persistent pruritis which is the earliest symptom in 3 or 4 per cent of all patients and may precede all other evidences by weeks or months. It is important to recognize that the symptomatology of Hodgkin's disease is a diverse one.

Clinical Forms of the Disease.—It is recognized that the characteristic pathologic changes may involve any organ in the body in which lymphoid tissue is present. Hence as almost universal involvement is possible, the clinical manifestations may be most varied and at times bizarre. In general it may be said that the clinical picture of the disease may be classified under the following forms:

1 Localized	6 Febrile
2 Generalized	7 Cutaneous
3 Mediastinal	8 Osseous
4 Abdominal	9 Nervous
5 Splenomegalic	10 Gastro intestinal

These clinical divisions are purely arbitrary but they serve to emphasize the protean manifestations of the disease and indicate that certain extensive involvement of various parts of the body may dominate the clinical picture. Rarely are the varieties entirely distinct as there is almost always a certain amount of overlapping with the symptoms of other types.

In any of the above types the division of Trousseau into the (1) latent, (2) progressive and generalized form, and (3) the cachectic stage is useful as most patients with the disease regardless of the clinical variety often progress to a certain extent through these three phases. In the common form of the disease the latent period is represented by the absence of symptoms until an enlarged and painless gland is discovered. The second period is characterized by an extension of the glandular involvement associated with complaints of weakness, loss of weight and ease of fatigue. During this period the lymphadenopathy is not always progressive for it may without treatment become stationary and the patient's general condition show pronounced improvement for brief intervals. The third stage is one of emaciation and heralds the fatal

the onset or shortly thereafter. *Some authors (13) have gone so far as* to consider that when the enlarged nodes first appear at the base of the left side of the neck the disease may have had its initial site internally and the neoplastic cells have been carried through the thoracic duct. If this were true there would be anatomical reason for the glands having appeared in the left cervical region. This view at present can be nothing more than interesting speculation. The following table from Slaughter and Craver (13) gives a list of the apparent primary sites of node involvement in their *series of 265 cases of Hodgkin's disease proven by biopsy*.

	Cases	*Per Cent*
Left neck	99	37.5
Right neck	19	6.8
Both sides of neck	18	6.8
Mediastinum	18	6.7
Right axilla	17	6.5
Left axilla	14	5.2
Left groin	10	3.7
Right groin	9	3.4

At the time the initial symptom is observed the patient is usually otherwise in good physical condition and has no additional complaints. Present day diagnosticians at once do a biopsy on such a gland and hence the nature of the malady is often definitely established early in the course of the disease *at a time when the patient is free from other complaints*. Under these circumstances it is difficult to believe that the patient has such a serious condition with an ultimately fatal outcome. There is eventually a progression of the involvement in the body and in turn the glands in the supraclavicular, axillary, subpectoral, mediastinal, retroperitoneal and mesenteric regions may become enlarged. The superficial lymph nodes are affected eventually in 95 per cent of all patients with this disease. The retroperitoneal glands show evidence of the disease in about 50 per cent and the mediastinal in 60 per cent.

On examination the superficial nodes are found to be round or slightly oval, non tender, with a smooth surface and are only loosely held together. The skin overlying them is not red. Never do they become adherent unless there is some complication such as tuberculosis, nor does a draining sinus form unless this complication is present. In consistency they are usually moderately firm but slightly elastic and hence the term rubbery has been employed as a descriptive one. In some instances they may even be soft. As the disease advances or following roentgen ray therapy they may become hard and sclerotic.

In some instances the glands may appear in unusual sites. They are occasionally seen along the margin of the sternum where they follow the line of the internal mammary artery. Rarely they appear in the occiput. One of my patients who was a diagnostic problem for some weeks

The studies of Jacox Peirce and Hildreth (*91*) at the University of Michigan showed that more than one half of the patients with Hodgkin's disease have evidence of pathology in the chest as indicated by the roentgen ray. The various changes have been divided into three main types as follows 1, tumor or adenopathy 2, parenchymal infiltration 3 pleural involvement with or without other intrathoracic involvement. The following data is from the table presented by Jacox, Peirce and Hildreth (*91*)

The total number of cases was 172 examined roentgenologically

(*a*) Patients with tumor or adenopathy	
(1) Hilar adenopathy only	19
(2) Mediastinal tumor	40
(3) Mediastinal tumor and hilar adenopathy	3
Total	62 (36%)
(*b*) Parenchymal infiltration	
(1) Parenchymal involvement only	4
(2) Parenchymal involvement with hilar adenopathy	4
(3) Parenchymal involvement with mediastinal tumor	7
(4) Parenchymal involvement with hilar and mediastinal tumor	3
Total	18 (10.4%)
(*c*) Pleural involvement with or without other intrathoracic lesion	15 (8.7%)

Intrathoracic Tumor or Adenopathy —The evidences of these changes range from localized perihilar or carinal lymph node enlargements to gross intrathoracic masses which occupy a large part of the thorax. The earliest roentgenographic signs of infiltration of the mediastinal lymphoid tissue is a flattening out of the profile of the supercardiac shadow usually bilateral with extension toward the thoracic outlet. When this change is examined by lateral projection it is obvious that the normal substernal space has been obliterated. As the condition progresses the pulmonary fields are displaced laterally with some tendency for the mass to extend along the upper bronchovascular trunks (91)

Parenchymatous involvement of the lung although not common is important because it may be mistaken for other forms of pulmonary pathology such as abscess tuberculosis primary bronchogenic carcinoma or metastatic neoplasm. A small percentage of these cases present parenchymal changes only and the remainder have associated hilar and mediastinal manifestations. The parenchymatous changes are at times diffuse resembling a pathologic change of an exudati
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termination of the disease It is almost invariably characterized by three *manifestations namely* (1) cachexia (2) fever and (3) anemia

Intrathoracic Changes —The changes which occur within the chest in patients with Hodgkin's disease are probably more common than is usually *stated in textbooks This is because there may be rather* extensive lesions in the lungs lymph glands or mediastinum which do not produce clinical symptoms or signs Furthermore necropsy studies indicate that some of the lesions are overlooked by *roentgenograms* of the chest because only one film has been taken during the long course of the disease Undoubtedly therefore there would be evidence of a greater incidence of intrathoracic involvement in patients with this disorder if the condition were investigated more completely by an increased number of roentgen ray examinations and more necropsies on patients with the disease

It should be emphasized that the available studies indicate very clearly that intrathoracic involvement is common and hence every patient with the disease or one who is suspected of having it should have careful roentgenographic studies of the chest by both anterior posterior and lateral projections

The lesions of Hodgkin's disease in the lungs have been classified *into five different groups by Verse (89) as follows* 1 *mediastinobronchial* node lesion with direct invasion of the lungs (a) by way of the hilum (b) through the medial surface of the lung 2 mediastinobronchial node lesions with peribronchial and intrabronchial spread 3 more or less lobar (diffuse) infiltration of the lung with varying degrees of involvement of the bronchomediastinal nodes 4 confluent lobular isolated circumscribed foci with bronchomediastinal nodes and 5 miliary (lymphohematogenous) foci with involvement in varying degrees of the bronchomediastinal nodes In the opinion of Verse probably more than 10 per cent of cases with pulmonary involvement are primary in the lung parenchyma This opinion which can only be based upon suggestive clinical and pathological evidence must be accepted with caution until further proof is adduced

The incidence and type of chest involvement is indicated by the studies of Vieta and Craver (90) who found intrathoracic involvement in 74 per cent of 411 cases of Hodgkin's disease The mediastinum was affected either by infiltration or nodules in 47.4 per cent, the parenchyma in 38.5 per cent the hilar nodes in 23.8 per cent the pleura by thickening in 7.4 per cent and by hydrothorax in 15.8 per cent Necropsy findings indicated that involvement was present in 88 per cent of the cases The lesions revealed by necropsy were 1 involvement of the mediastinum with or without hilar changes 74 per cent 2 changes in the parenchyma of the lungs 47 per cent 3 involvement of the parietal pleura 29 per cent and 4 *no lesions in the chest 12 per cent*

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Pleural involvement with or without other intrathoracic manifestations may be present in a relatively small per cent of patients with Hodgkin s disease It should be emphasized that any pleural reaction of obscure causation with or without other thoracic lesions should suggest the possibility of a change due to malignant lymphoma

It should be kept in mind that the roentgen ray findings in the thorax in patients with Hodgkin's disease are far more common than the symptoms and signs would indicate. Although the changes can be classified into various groups, it must be admitted that there are no pathognomonic roentgenological signs of the disease. Nevertheless roentgenograms of the chest are an excellent diagnostic aid in recognizing the condition. The roentgenological appearance offers no criteria of the duration of the disease.

The Splenic Type of Hodgkin's Disease.—The splenic Hodgkin's disease is spoken of when the primary or most advanced lesion occurs in this organ. From a clinical standpoint the term is used rather loosely when referring to a patient with the condition in whom the splenic enlargement is the most prominent clinical feature among all of the manifestations presented. Occasionally a patient is observed in whom the evidences of the disease are fever, a normocytic anemia, and moderate splenomegaly. In some instances early in the course of the disease there may be no superficial lymph gland enlargement; in fact, it may in some cases be absent through the course of the illness. According to Ewing (*4*), the primary splenic lesion is rare, some authors denying its existence. Yet undoubtedly cases have been described. In some instances, however, those cases which resemble primary Hodgkin's disease eventually prove to be splenic neoplasms.

A case is reported by Krumbhaar (*17*) in which there was Hodgkin's disease of the spleen and bone marrow without apparent involvement of the lymph glands. In this patient the spleen extended to the level of the anterior superior spine. The red blood cell count was 1.07 millions per cubic millimeter and the white blood cell count 8200 per cubic millimeter. The spleen at necropsy weighed 1090 grams and measured 22 x 16 x 7 cm. The histologic appearance was typical of Hodgkin's disease.

Secondary invasion of the spleen is frequently observed and occasionally, as previously emphasized, the splenomegaly may be the most striking clinical feature of a patient with the disorder. The primary lesion in such instances may be in superficial nodes or in the deeper, mainly the retroperitoneal chains. Some of the patients with the Pel-Ebstein type of fever are in this group.

According to Gall and Mallory (*2*) the spleen is enlarged in 45 per cent of all cases of patients with Hodgkin's disease. Boyd (*92*) states that splenomegaly is present in 60 to 65 per cent of the cases. It should be emphasized, however, that the organ is rarely palpable early in the course of the disease. I am in accord with the opinion of Goldman (*78*) who states that *one should hesitate to make a diagnosis of Hodgkin's disease in a patient with a palpable spleen who appears to be in good health.* In the advanced cases, however, this feature is helpful in confirming the diagnosis. In Goldman's series of 212 cases splenomegaly was noted

in only three and hepatomegaly in only one of the 89 *early cases* of the group On the other hand in the 123 *advanced cases* the spleen and liver were palpable in 64 and 45 cases respectively

Fever in Hodgkin's Disease and the Febrile Form of the Disorder—Although some textbooks state that fever is present in only 50 per cent or less of all patients with Hodgkin's disease in my experience this has been an underestimate as it has usually been observed in *all* patients at some time during the course of the illness The febrile reaction may be said to be of three general types namely 1 An intermittent or remittent variety in which the temperature reaches the vicinity of about 101 degrees (F) in the evening and is appreciably lower or normal in the morning In some instances the temperature curve may be characteristic of the septic type of fever 2 The Pel Ebstein febrile reaction which has been reported to occur in about one third of the patients with the disease has been encountered much less frequently in my experience This form of febrile curve is highly characteristic and when present should at once suggest the diagnosis of Hodgkin's disease It may be described as a febrile curve in which over an interval of five or six days the temperature rises until it reaches a maximum of 103 to 105 degrees (F) after several days at this level when there is but little remission in the curve there is a gradual decline of the fever until it reaches normal in a period of another five or six days The entire febrile episode is usually included in 14 to 18 days Following this the temperature remains normal for a week to 10 days and the febrile cycle is again repeated in the characteristic manner These cycles of fever alternating with periods of normal temperature may continue for months In some patients on each day that the body temperature rises chilly sensations or an outspoken rigor may be experienced (3) Continuous fever This usually occurs late in the course of the disease and should be regarded as an ominous sign from a prognostic standpoint for it usually portends a steadily down hill course for the patient The temperature may rise to a height of 100 to 103 or 104 degrees (F) and not reach normal at any time in the 24 hour period of the day Such a febrile reaction is usually associated with an anemia and cachexia which heralds a rapidly approaching fatal termination

In some patients with Hodgkin's disease the only manifestation of the disease for a considerable period of time may be some sort of febrile reaction It may be a slightly irregular fever a septic type of temperature curve or the classical Pel Ebstein form When fever of either type occurs before other symptoms or signs are apparent it usually creates a most difficult diagnostic problem This is often not solved unless the Pel Ebstein curve suggests the diagnosis or until a gland becomes enlarged and is accessible for biopsy purposes *Certainly in all patients who present the clinical picture of fever without obvious*

explanation the possibility of Hodgkin's disease should be given careful consideration Biopsy of an inconspicuous gland which has previously been overlooked in some instances may solve the problem

Anemia, Leukopenia, and Pel Ebstein Fever in Hodgkin's Disease — *It is pointed out by Riley and Gailland (93) that the association of anemia leukopenia and Pel Ebstein fever although not common in* Hodgkin's disease is important for two reasons first it is indicative of primary or principal involvement of abdominal lymphoid structures second the chief clinical manifestations may present a difficult diagnostic problem because in 62 per cent of such cases there may be no superficial lymphadenopathy by which the diagnosis could have been facilitated *by lymph node biopsy*

Cutaneous Manifestations —*Involvement of the skin has been estimated* to occur in 15 to 40 per cent of all cases of the disease In my experience the most common cutaneous involvement has been a severe and intractable itching which may precede in some cases all other evidences of the disorder by several weeks or months In others it may occur at the same time or it may follow the appearance of other characteristic *findings such as lymphadenopathy Certainly the presence of a severe* generalized pruritis alone or in association with lymphadenopathy should arouse suspicion that one is dealing with some type of malignant lymphoma which is most frequently of the Hodgkin's type

Pruritis may exist without apparent alterations in the appearance of the skin or in combination with various cutaneous morphological lesions *In Hodgkin's disease especially it may be associated with a progressive bronzing of the skin which is more pronounced* in the axillary or gluteal regions The cause of the pruritis is obscure but a number of different theories have been suggested none of which has received general acceptance The various theories offered are as follows 1 That the condition is due to an actual microscopic infiltration of the skin with neoplastic cells of Hodgkin's disease *This is not accepted by all because it is not agreed that the disease is neoplastic in nature* Furthermore there has not been a sufficient number of carefully studied cases by means of biopsy to confirm this explanation 2 It has been suggested that the itching arises from toxic substances formed in the lymph nodes This may be true but there is no positive proof of it It has been offered as an explanation largely *on the grounds that some believe that there* are no structural changes present to explain the symptoms 3 It has been considered by some that the pruritis may be on the basis of changes in the sympathetic nervous system or due to a radiculitis

Following pruritis without specific changes in the skin the next most commonly occurring cutaneous lesion of Hodgkin's disease is the so called exfoliative erythroderma *It is characterized by* a generalized erythroderma exfoliation, and infiltration which may involve the skin of the en

ture body With the progression of the lesion the skin becomes hyper pigmented inelastic and of a leathery consistency usually associated with a distressing pruritis It is always wise to suspect that cases of exfoliative dermatitis which do not respond to the usual therapeutic meas ures may be on the basis of Hodgkin s disease

The nature of the pathologic changes causing exfoliative dermatitis is in dispute By some it is held that the condition is a specific lesion and that lymphoma cells can be demonstrated in the skin Others claim that it is a toxic state and that specific dermatologic alterations are not pres ent Certainly additional careful studies which include more biopsies of the skin are needed before a definite answer can be given to this question

Various other types of cutaneous involvement have been reported as occurring in this disorder and have been designated toxic rashes This group includes erythemas maculopapular morbilliform eruptions ecze mas and other non specific entities The mechanisms producing these lesions are unknown

Herpes zoster occurs in about 2 5 per cent of all cases of Hodgkin s dis ease Various theories as to the causation of this complication are (1) that it is due to nerve irritation (2) that it results from pressure on a nerve by tumor tissue and (3) that toxic products from the lymphoma produce a parenchymatous neuritis

Mycosis Fungoides —The present view concerning this skin manifesta tion is that there is no clinical or pathological basis for considering this condition a disease entity Most cases of this cutaneous manifestation have been seen either in patients with Hodgkin s disease lymphosarcoma or lymphatic leukemia The common form develops on the basis of a pre mycotic lesion of which the most frequent type is a desquamative dermati tis with pruritis In some instances the premycotic lesion may precede the formation of tumor for months or years On the other hand cutaneous tumors may be the first sign of a lymphoma In general the tumors are raised purplish red areas of infiltration which exceed three cubic milli meters in diameter Ulceration occurs late in the course of the disease

Changes in the Bones —Involvement of bone is usually said to occur in between 10 and 20 per cent of all patients with Hodgkin s disease If roentgen ray examination is done only on the patients who complain of pain or have deformity the lower figure of incidence will be found If a greater number of routine studies are done however there will be a higher incidence of involvement discovered This is because definite lesions of this type may be present without causing symptoms for a con siderable period of time In rare instances the osseous involvement may be the first clinical evidence of the disease as it may occur even before there is enlargement of the superficial lymph nodes In such patients the true nature of the pathologic process in bone is usually overlooked and such changes are usually considered erroneously to be metastases

from a primary carcinoma located at some undiscovered site elsewhere in the body

Recently Steiner (*60*) has investigated the absolute incidence of lymphogranulomatous involvement of the marrow in cases of Hodgkin's disease by the microscopic examination of random small samples of various bones selected at necropsy. It was found that in one or more sections in 11 of 14 consecutive cases of Hodgkin's disease (78.6 per cent) there were lymphogranulomatous foci. It was the opinion of this observer that practically every case of the disease would show osseous involvement if a sufficient number of bones could be examined thoroughly. He considered that the widespread skeletal involvement might explain why patients with Hodgkin's disease often experience generalized pains but he did not believe that such changes served as a basis of the anemia on a replacement basis in the average case. He considered that the nature of the bone changes were such that aspiration of marrow for diagnostic purposes would be likely to result in failure.

Although Steiner studied only 14 cases it is of interest to consider the frequency with which the various bones were found to be involved. His findings expressed in the percentage that were positive were as follows: dorsal vertebral body 85.8 per cent, lumbar vertebral body 74.[illegible] per cent, ilium [illegible].6 per cent, sternum 63.4 per cent, rib 57.1 per cent, clavicle 50 per cent, metatarsal and frontal bones no involvement.

In a review of 269 cases in 92 papers dealing primarily with osseous involvement in lymphogranuloma, Steiner found the sites of osseous lesions in lymphogranulomatosis to be as follows: vertebra 196 cases, pelvis 81 cases, rib 67 cases, femur 43 cases, sternum 42 cases, skull 24 cases, humerus 15 cases, clavicle 11 cases, scapula nine cases, tibia eight cases, mandible one case, maxilla one case, radius one case, os calcis one case.

In an attempt to determine the incidence of bony lesion in Hodgkin's disease a group of 2006 cases were studied by Steiner from a clinical standpoint as reported in the literature and the average incidence was found to be 8.3 per cent. The greatest frequency of osseous involvement in different series of cases was 15.7 per cent and the lowest 0. He also found that in 547 unselected necropsies in cases of Hodgkin's disease the frequency of bone lesions averaged 28.3 per cent. He points out however that here again is a great variation in the incidence of bony lesions depending on the thoroughness of the examination of the skeleton. The rate was low when the skeleton was examined only where there were indications from the clinical and roentgenological findings and high when the inspection of the skeleton was routine and thorough.

From a review of the literature this author concludes that in Hodgkin's disease the lesions in bone may involve practically any part of the skeleton although there are sites of predilection that bone at times seems to be

the primary site of origin of the disease that the lesions may show great variations in the gross morphological characteristics and clinical effects mimicking at times other lesions of bone both primary and secondary in many different diseases

The bones most commonly affected are the vertebrae The lesion may occur anywhere in the spine but the bodies of the vertebrae in the dorsal and lumbar regions are most commonly involved Collapse of the vertebral bodies may occur but almost always the intervertebral discs are spared In addition to the vertebrae the most commonly involved bones in order of frequency are the pelvis ribs upper ends of the femurs and the sternum Less frequently are the ends of the humeri and the other long bones and the skull affected When the process is present in the long bones the deposits are usually in the proximal and distal thirds It is of interest as Goldman (78) states that the portion of the bone most commonly involved corresponds to the actively hematopoietic portion of the bone marrow

There is no absolutely typical roentgenological picture of the bone change in Hodgkin s disease The process is largely osteolytic and resembles a carcinomatous lesion although osteoblastic changes may occur and in some instances the two processes may be associated In general it may be said that the osseous lesions of Hodgkin s disease are less painful and more sensitive to the roentgen ray than those of carcinoma

The exact mode of involvement of bone is not known It is of importance to note as previously stated that the portion of bone most commonly affected corresponds to the part in which there is the most active hematopoiesis Furthermore the pathologic process of Hodgkin s disease is known to be present in the bone marrow in at least 40 per cent of the cases according to Ziegler (94) and this must be regarded as an underestimate It is possible that the osseous change may arise from foci in the marrow On the other hand there is suggestive evidence which indicates that in some cases at least the disease process may spread to bone from a contiguous diseased lymph node

Treatment of the bone complications is most beneficially accomplished by means of the roentgen ray In almost all instances there is prompt relief from pain and in some patients a remarkable reparative process may be demonstrated In one of my patients previously mentioned there was a most surprising recovery from an extensive bony involvement which has now continued over a period of 10 years This patient a male of 40 years had extensive destruction of the 4th 5th 6th and 7th cervical vertebrae and a portion of the scapula In addition there was striking enlargement of the glands of the mediastinum Biopsy of a gland in the neck showed what was interpreted as Hodgkin s disease of the sarcomatous type Following roentgen ray therapy there was a remarkable recalcification of the bony lesions and a striking diminution in the enlarged glands of the medi

astinum The patient has been under observation now for over 12 years and has no complaints except a stiff neck due to the ankylosis associated with the reparative process in the cervical vertebrae

Hodgkin's Disease of the Central Nervous System—Involvement of the cerebrum cerebellum meninges cranial nerves or spinal cord occurs in 10 to 15 per cent of all patients with the disease In almost all instances the nervous system is affected secondarily A primary lymphogranulomatosis however of the lymph elements in the connective and fatty tissue in the epidural space within the spinal canal has been described

Gray and his collaborators (95) after a survey of the literature conclude that secondary changes may occur as the result of any one of the following different mechanisms

1 In a small number of cases there is direct invasion of the vertebrae from the lymph glands adjacent to the spine This may cause vertebral collapse and direct mechanical pressure on the spinal cord

2 The most common cause is an extension from retroperitoneal mediastinal and intrathoracic masses by way of the lymph spaces of the nerve roots through the intervertebral foramina and into the epidural space Large epidural deposits of lymphogranulomatous tissue are formed in this area These either completely or partially encircle the spinal cord thereby producing compression

3 There may be extension of the lymphogranulomatous tissue from the epidural to the subdural space

4 The spinal cord changes may be due to the mechanical obstruction of the blood vessels which accompany the spinal roots whether within the intervertebral foramina or just outside the cord thus interrupting the vascular supply and producing thromboses of the vessels and typical myelomalacia

5 Occasionally the spinal cord may show definite areas of degeneration of obscure etiology These have been attributed to (a) a definite infectious myelitis and to (b) obstruction of the subarachnoid space around the nerves by large masses of arachnoidal cells which arise from a proliferation resulting from a non specific reaction of the pia arachnoid This reaction is attributed to the irritation of the epidural growth The obstruction thus caused blocks the principal avenues of escape of the spinal fluid and causes a damming back of the tissue fluids into the parenchyma of the spinal cord with subsequent cord damage

6 In occasional cases various tract degenerations appear within the spinal cord without obvious explanation It has been suggested that they may be due to anemia and partial anoxemia In some cases if an achlorhydria is present I would suggest the possibility of some vitamin deficiency perhaps in some component of the B complex group as an etiological factor

7 Lymphogranulomatous deposits in the lymph spaces or on the meninges of the brain may account for cerebral symptoms including convulsive attacks It has also been suggested that these same symptoms may arise from cerebral edema secondary to obstruction of the veins of the neck and upper thorax by enlarged cervical or mediastinal glands

Symptoms and Signs of Neurological Involvement —These manifestations may be most diverse depending on the extent and site of the lymphoblastomatous lesions The symptoms may be motor sensory cerebral cauda equinal or nerve root in nature In some patients the changes are a spastic paralysis from pyramidal tract involvement while in others ataxia and incoordination from lesions affecting the posterior columns of the cord are observed

A complete transverse spinal cord lesion with motor and sensory loss below its segmented level is the usual neurological manifestation In some instances the outstanding symptom is severe pain as in sciatic or brachial neuritis which is due to nerve root involvement or occasionally to pressure of the epidural infiltration against the thalamic tract (95) or the pain may be due to destructive lesions of the vertebrae or pelvis Other neurological complications which have been observed are generalized increased intracranial pressure facial palsy deafness dysphagia and sphincter difficulties due to conus or cauda equina lesions

In some instances spinal puncture done below the block in the spinal canal will show the usual findings of xanthochromic spinal fluid increase in its protein content and pleocytosis Also there will be decreased pressure without a response to jugular compression

In an extensive review of the subject Sparling Adams and Parker (96) state that in lymphomatous disease of the nervous system there are four outstanding clinical syndromes *First* and the one most frequently encountered is caused by an acute or subacute compression of the spinal cord They emphasize that the rapid development within a few days to a few months of a paraplegia with corresponding sensory loss and sphincter paralysis in association with pain in the back or radicular pains should always suggest the possibility of a spinal epidural lesion of a lymphomatous nature *Second* a symptom complex characterized by involvement of the trigeminal abducens facial auditory or glossopharyngeal nerves in combination with headache drowsiness convulsions and other evidence of cerebral cortex involvement Usually x rays of the skull will show evidence of bone destruction *Third* evidence of meningeal invasion with or without cranial or spinal nerve or cerebral involvement The chief associated complaints are usually headache neck rigidity and nausea and vomiting The *fourth* clinical condition is a primary cerebral lymphoma Such a condition has never been observed to be due to Hodgkin s granuloma but it is associated with Hodgkin s sarcoma or reticulum cell sarcoma of the brain Mental confusion stupor coma without much

papilledema or elevation of pressure in the spinal fluid are the characteristic findings

The principles involved in the treatment of such lesions of the central nervous system are first craniotomy or laminectomy as the case may be with biopsy removal if possible of any lymphoblastomatous material followed by roentgen therapy The prognosis of course is not good the outcome depending on the accessibility of the involvement to surgery and roentgen therapy and the general condition of the patient The value of nitrogen mustard therapy in such patients is unknown at present Such treatment however should be given consideration in all patients with neurological involvement as the lesion may be more accessible to this form of treatment than it is to x ray therapy

Involvement of the Gastro intestinal Tract—Within recent years there have been an increasing number of cases reported in which Hodgkin s disease has involved the gastro intestinal tract Undoubtedly, in the past this condition has been overlooked in some cases both by the clinician and the pathologist The clinical picture has most often been confused with chronic ulcerative colitis especially the tuberculous variety with gastric carcinoma and with bowel obstruction The pathologist from examination of the gross specimens is likely to regard the condition as lymphosarcoma tuberculosis or carcinoma

The most outstanding clinical manifestations are diarrhea abdominal pain rapid wasting a pronounced normocytic and hypochromic anemia leukopenia or a normal white blood cell count and fever The diarrhea is often profuse and watery but loss of blood from the bowel has not been commonly observed It is usually the complaint of abdominal pain which directs the attention of the clinician to the gastro intestinal tract The condition has been most frequently observed in the fifth and sixth decades of life

According to Hayden and Apfelbach (97) the main obstacles to a correct diagnosis are the infrequency of the disease the lack of specific diagnostic tests for Hodgkin s disease except histologic examination the multiplicity of the gastro intestinal alterations and the lack of enlargement of the superficial lymph nodes and the spleen

The characteristic change which is observed is the presence in the gastro intestinal tract of gray translucent lymphoid tissue which frequently undergoes ulceration The individual areas of infiltration vary greatly in size some being no larger than a few millimeters in diameter whereas others extend over long portions of the gastro intestinal tract In general it may be said that the pathological changes characteristic of this condition are of two types The most common is one in which there are multiple small ulcers of the stomach and bowel The other is represented by infiltration of the wall in the areas affected Rarely does the latter cause obstruction of the bowel but this complication has been observed In most instances multiple areas of the gastro intestinal tract are involved

The order of frequency in which the pathologic changes occur in various parts of the gastro intestinal tract is as follows stomach jejunum ileum colon and rectum Lymphomatous involvement differs from tuberculous as the former most commonly affects the proximal portion of the gastro intestinal tract

The *most common causes of death are cachexia perforation of the intestinal tract and occasionally anemia from hemorrhage*

It is emphasized by Holmes (88) that the lesions are usually multiple a fact which is of considerable value in differentiating them from other gastro intestinal tumors He also states that a common site for such tumors is in the stomach in the region of the pylorus or ileocecal valve When the lesion is in the stomach there is also frequently an accompanying one in the duodenum or upper portion of the small bowel The roentgen appearance of lymphoma of the Hodgkin s type is not characteristic and the findings are often mistaken for carcinoma which it closely resembles The change of greatest importance which should at once suggest the possibility of *Hodgkin s disease is a multiple lesion* especially one involving both the stomach and the duodenum The lesion in the stomach resembles carcinoma and that in the duodenum suggests ulcer In Holmes experience typical gyroscopic rugae have been present in a high percentage of cases and have been found only once in cases in which lymphoblastoma was not present

Pregnancy in Hodgkin s Disease—In a comprehensive review of the subject (98) Kasdon states that in women Hodgkin s disease does not affect ovulation fertility the incidence of spontaneous abortion or ante intra or postpartum hemorrhage Furthermore he believes that the obstetrical aspects of gestation parturition and the puerperium are not influenced by coincidentally associated Hodgkin s disease It is his opinion that the possibility of placental transmission of the disorder to the fetus must be considered as in three of the reported instances of Hodgkin s disease in young infants the presence of the disorder in two of the mothers is unquestioned On the other hand all other reports of viable children born of mothers with the disease have been said to be free of the disease There is no instance reported of lymphoma involving the placenta or membranes Nevertheless Kasdon (98) concludes that Hodgkin s disease is transmitted from mother to fetus across the placenta in 9 per cent of the cases It is my own opinion that fortuitous circumstances have not been excluded in these cases and it would be necessary for me to have incontrovertible proof of placental transmission before accepting it

Of further interest is that Kasdon (98) was unable to find a report in which there was injury to the shielded fetus from roentgen irradiation used in the treatment of Hodgkin s disease I do not know of any published experiences at the present time bearing on the effect of the nitrogen mustards on the fetus when the mother is treated with this agent Never

theless, the application of roentgen ray therapy to pregnant women, in my opinion, is a definite risk to the status of the fetus and its use should be considered inadvisable or, if employed, the possible hazard should be kept in mind. The same tentative although unproven possibility should be applied to the nitrogen mustards.

It is stated by Summers and Reid (99) that 49 infants have been borne of mothers with Hodgkin's disease and reported in the literature. They add the case of a mother with the condition who has borne two more healthy children without an untoward result.

Is a pregnancy likely to induce an exacerbation of existing Hodgkin's disease in a woman in whom the condition is quiescent? This is a difficult question to answer definitely, as some aspects of the spontaneous course of the disease are uncertain. It is stated by Kasdon (98) that such an exacerbation occurred in 18 of 42 such gestations observed, but that this is no more than would be anticipated in the usual course of the condition in non-pregnant women. On the other hand, Portmann and Mulvey (*100*) conclude that pregnancy may be responsible for such an exacerbation. It is difficult, however, to understand how these authors could be certain that such flare-ups were not incidental in the natural course of the malady.

It is stated by Kasdon (99) that an interruption of pregnancy during the course of Hodgkin's disease is not indicated from the evidence at hand. I share this opinion. If confronted with a patient who had Hodgkin's disease and was pregnant I would hesitate to employ roentgen ray therapy and use careful shielding if it was concluded that such treatment was imperative. In general, I would endeavor to rely on general therapeutic measures which could not possibly harm the fetus, including repeated blood transfusions. As previously stated, the effect of nitrogen mustards on the fetus *in utero* is unknown at present.

Amyloidosis in Hodgkin's Disease.—Attention is directed by Wallace and his associates (*101*) to the occurrence of amyloidosis in patients with Hodgkin's disease. Although this is not mentioned frequently in textbooks and monographs on the subject, it is a relatively common complication in the advanced stages of the disease. These authors collected 35 cases from the literature in which the two diseases co-existed and report an additional case with the necropsy findings. From their experience they conclude that the amyloidosis complicating Hodgkin's disease is always of the secondary type, involving the liver, spleen, kidneys and adrenals. This is in contradistinction to primary amyloidosis which usually is found chiefly in the heart, lungs, skin, mucous membranes and tongue.

Of the reported cases of secondary amyloidosis in Hodgkin's disease 80 per cent had hepatomegaly and 65 per cent splenomegaly, but these changes cannot be used to determine the presence of amyloidosis in the

malady as they also occur in Hodgkin's disease uncomplicated by amyloidosis Edema ascites and pleural effusion are commonly encountered in secondary amyloidosis due to the hypoproteinemia which results from the albuminuria of renal amyloidosis The authors conclude that the presence of proteinuria and significant absorption of Congo red (60 to 100 per cent) are the most reliable criteria for determining the presence of secondary amyloidosis in the disorder

The Blood Changes in Hodgkin's Disease —Most hematologists *agree that although there is a tendency to* certain changes *in the* blood of patients with Hodgkin's disease these are *usually not of great diagnostic importance* The controversy which has been debated since the reports of Bunting dealing with this question in 1911 and 1914 (*102*) can be more easily understood if one considers the following points which may explain the differences of opinion which have arisen

In some instances conclusions regarding the differential white blood cell count have been based upon the results reported by other than skilled hematologists in which commonly as few as 100 white blood cells have been counted Obviously in determining the small but significant changes which may be present in patients with this disease such results cannot be employed as a basis for discussion Also it is undoubtedly true that some reports of the blood may have been based upon an examination after irradiation and in others before treatment Other factors which might have had an influence in changing the blood count are concomitant infections the stage of the disease and the placing of too much dependence on single rather than multiple blood examinations

The fluctuation in the differential formula of the white blood cells from day to day is well illustrated by the observations by Boyer (*103*) He pointed out the rather striking variations in the 52 complete blood counts which were made on a patient with Hodgkin's disease over a period of four months It was emphasized that had only one blood count been done on the patient it might have been performed at a time when the mononuclears were entirely absent or when they were increased and also at a time when the immature cells could have led one astray in the diagnosis The continued study in his patient indicated a tendency toward an increase in mononuclear cells and polymorphonuclear cells

If due care is taken to eliminate all of the above possible causes for variation then I believe that it is possible to say that certain changes are commonly present in the blood of patients with this disease *but these are usually not extensive and hence are of only slight value from a diagnostic standpoint* Certainly it can be said that they are not pathonomic of the condition

The total white blood cell count in untreated patients is within the accepted limits of normal (6000 to 10 000 per cubic millimeter) in about one half of the cases and below or above normal in 25 per cent of the cases, respectively

In some instances there may be a striking leukopenia with the count below 2000 per cubic millimeter or even lower, but the exact significance of this is not known. By some it is taken as evidence of extensive involvement of the mediastinal or abdominal glands but this is denied by others. The entire subject of leukopenia in Hodgkin's disease has been reviewed by Boyer (*103*) who found references to patients in whom the white blood cell count has been below 1000 per cubic millimeter. In most instances however these patients had received high voltage roentgen ray treatments. Occasionally however there is striking leukopenia which occurs without reference to any form of therapy. It is usually associated with a severe anemia and is probably indicative of a poor prognosis as it suggests that the bone marrow has been involved extensively. In the case reported by Boyer (*103*) there was atypical Pel Ebstein fever, a persistent and severe leukopenia and an extremely marked anemia. Prior to death the physical examination gave no suggestion of Hodgkin's disease save the palpable spleen, as the superficial lymph nodes were not enlarged. It must be concluded at present that the cause and significance of leukopenia in this disorder are not clear.

The leukocyte count may be increased up to 20 000 per cubic millimeter or even higher in a small per cent of patients but the explanation of this is not known. There is a distinct tendency to an increase in the neutrophils especially when the absolute neutrophil count is considered and when the normal is taken as 5000 of these cells per cubic millimeter. Likewise there is not infrequently an absolute increase in the eosinophils over the normal count of 400 per cubic millimeter. Recently Williams and Neubuerger (*104*) have reported the case of a 73 year old woman with Hodgkin's disease who had a white blood cell count which was as high as 140 000 per cubic millimeter with 52.3 per cent eosinophils. The diagnosis was confirmed by necropsy. From the literature they conclude that an eosinophilia of some extent is observed in 5 to 20 per cent of all patients with the disease. In practically all instances in which there is an increase in the eosinophils there is also a leukocytosis. They found that leukocyte counts varying from 8000 to 11 000 per cubic millimeter with 20 to 50 per cent eosinophils to a white blood cell count as high as 105 000 per cubic millimeter with 90 to 99 per cent eosinophils are representative of the extremes of the total counts and the eosinophil percentage. The significance of an eosinophilia in the disease is not known. Some relate it to pruritis and others to intestinal involvement but this has not been supported by definite proof. Krumbhaar (*11*) states with reference to the eosinophilia that These cells should not necessarily be regarded as a fundamental part of the Hodgkin's process but rather as a response widely differing in different cases to a hypothetical substance that attracts and stimulates the eosinophils.

Undoubtedly the most common alteration in the blood in patients with this disease is the decrease in the lymphocytes and increase in the

monocytes It is not uncommon to find the number of lymphocytes below the normal of 1500 per cubic millimeter and the monocytes increased above 700 per cubic millimeter

Anemia —Almost all patients develop an anemia at some time during the course of the disease The most common type observed in 49.5 per cent of our cases having an anemia is the *hypochromic variety with or without microcytosis* This is similar to the anemia of iron deficiency in patients with Hodgkin s disease The administration of iron is rarely beneficial and hence in this respect it resembles the anemia of chronic infection A much smaller per cent about 8 4 in our cases with anemia, have a *normocytic normochromic variety* which suggests the possibility that the lymphoblastomatous process has invaded the bone marrow It is refractory to all forms of therapy except blood transfusions or measures directed toward the underlying lymphoblastomatous process A *macrocytic anemia* was present in 6 0 per cent of our patients with anemia and this was either hypochromic or normochromic in nature This may be observed in association with a high per cent of reticulocytes in the circulating blood which is seen in patients with Hodgkin s disease who occasionally have a hemolytic anemia.

The anemia is usually present in the moderately or far advanced cases of Hodgkin s disease It is rarely severe averaging 2.5 to 3.5 million red blood cells per cubic millimeter with a hemoglobin between 8.2 to 11 0 grams per 100 cc The red blood cells do not ordinarily display pronounced anisocytosis or poikilocytosis Nucleated red blood cells rarely appear in the blood

An *acquired hemolytic anemia* related to the Hodgkin s disease process is occasionally observed It was present in three of our 148 patients In one patient a young girl with a diagnosis of Hodgkin s disease proven by biopsy the hemoglobin was 4.2 grams the red blood cell count 1.2 million per cubic millimeter the mean corpuscular volume 129 cubic microns and there was increased fragility of the erythrocytes Spherocytes were not present The literature dealing with hemolytic anemia in Hodgkin s disease has been reviewed by Brown and Meynell (*105*) who report a case of their own They regard the condition as uncommon but state that the incidence is probably greater than the number of reported cases suggest The patient they studied was a 56-year-old male with Hodgkin s disease confirmed by biopsy He had a red blood cell count of 1,250 000 per cubic millimeter and a hemoglobin of 3.2 grams with increased fragility of the erythrocytes a reticulocyte count of 11 per cent and a weakly positive direct Coombs test Splenectomy depressed the hemolytic process temporarily

In summary therefore it may be said that the changes in the white blood cells of the peripheral blood are often minor in extent and are present inconstantly They cannot be considered as diagnostic of the disease

In some instances there may be a striking leukopenia with the count below 2000 per cubic millimeter or even lower but the exact significance of this is not known By some it is taken as evidence of extensive involvement of the mediastinal or abdominal glands but this is denied by others The entire subject of leukopenia in Hodgkin s disease has been reviewed by Boyer (*103*) who found references to patients in whom the white blood cell count has been below 1000 per cubic millimeter In most instances however these patients had received high voltage roentgen ray treatments Occasionally however there is striking leukopenia which occurs without reference to any form of therapy It is usually associated with a severe anemia and is probably indicative of a poor prognosis as it suggests that the bone marrow has been involved extensively In the case reported by Boyer (*103*) there was atypical Pel Ebstein fever a persistent and severe leukopenia, and an extremely marked anemia Prior to death the physical examination gave no suggestion of Hodgkin s disease save the palpable spleen as the superficial lymph nodes were not enlarged It must be concluded at present that the cause and significance of leukopenia in this disorder are not clear

The leukocyte count may be increased up to 20 000 per cubic millimeter or even higher in a small per cent of patients but the explanation of this is not known There is a distinct tendency to an increase in the neutrophils especially when the absolute neutrophil count is considered and when the normal is taken as 5000 of these cells per cubic millimeter Likewise there is not infrequently an absolute increase in the eosinophils over the normal count of 400 per cubic millimeter Recently Williams and Neubuerger (*104*) have reported the case of a 73 year old woman with Hodgkin s disease who had a white blood cell count which was as high as 140 000 per cubic millimeter with 52 3 per cent eosinophils The diagnosis was confirmed by necropsy From the literature they conclude that an eosinophilia of some extent is observed in 5 to 20 per cent of all patients with the disease In practically all instances in which there is an increase in the eosinophils there is also a leukocytosis They found that leukocyte counts varying from 8000 to 11 000 per cubic millimeter with 20 to 50 per cent eosinophils to a white blood cell count as high as 105 000 per cubic millimeter with 90 to 99 per cent eosinophils are representative of the extremes of the total counts and the eosinophil percentage The significance of an eosinophilia in the disease is not known Some relate it to pruritis and others to intestinal involvement but this has not been supported by definite proof Krumbhaar (*11*) states with reference to the eosinophilia that These cells should not necessarily be regarded as a fundamental part of the Hodgkin s process but rather as a response widely differing in different cases to a hypothetical substance that attracts and stimulates the eosinophils

Undoubtedly the most common alteration in the blood in patients with this disease is the decrease in the lymphocytes and increase in the

injection of a broth suspension prepared from diseased lymph nodes from patients with Hodgkin's disease. It was suggested by Gordon that the effects were the results of the action of a virus but this has not been substantiated by other observers. Many workers have stressed its value as a diagnostic test in obscure cases although there is not a uniform opinion concerning its usefulness.

Steiner (*109*) has given an excellent review of the literature dealing with the test and presented the results of his own investigations. He found that the reaction was positive in 76.2 per cent of 21 cases of Hodgkin's disease proven by the examination of tissues. According to him of 310 cases previously reported in the literature the test was positive in 229 (73.9 per cent). In his experience with 40 control (non lymphogranulomatous) lymph glands there were no positive reactions while in the 452 control cases collected from the literature positive reactions were reported in only eight (1.77 per cent). The Gordon reaction therefore appears to be of some value in the diagnosis of the malady but it should of course be accompanied by histological examination of the lymph glands. In the opinion of Steiner the test shows uncanny ability in differentiating closely allied types of lymphadenopathy. He considers that the distribution of the Gordon agent is such as to make it unlikely that it is the cause of the disease. Its properties are those of a non living agent possibly enzymatic. It should be concluded therefore that the test while reliable in about three fourths of the cases is not specific.

Within recent years there has been a tendency to associate the type of reaction with the presence or absence of eosinophils in the lesions. It is held by some that false negatives were apt to be in those cases that did not show any eosinophils in the lymph glands used for inoculation. Furthermore it has been claimed that the activating agent is connected with the presence of eosinophilia either in Hodgkin's disease or some other disorder. According to Krumbhaar (*11*) the test is of no more diagnostic significance than is the more easily acquired estimate of the eosinophils in the lesions and in the blood stream.

Treatment.—Roentgen ray therapy is the standard method of treatment and its use should be considered in all patients. There is ample evidence to indicate that a large proportion of the patients will be restored temporarily to an apparent state of health and in individual cases it undoubtedly prolongs life. It seems fair to say in all except advanced cases there is some improvement following irradiation. Our experience at the University of Michigan indicates clearly that with appropriate treatment the life of the average patient is prolonged by such therapy (*91*).

It is my opinion that roentgen therapy should be regarded as a suppressive type of therapy and one which will not completely eradicate the

Nevertheless when a careful blood examination is done there are frequently certain rather slight but at the same time definite alterations in the white blood cells These are a lymphopenia with a monocytosis and in some instances an eosinophilia As the disease advances the percentage of neutrophils may increase Many patients have some of these changes present and it is estimated that in about 25 per cent they are all co existent In addition almost all patients develop a moderate to severe anemia which is most commonly hypochromic with or without microcytosis rarely it is macrocytic occasionally it is hemolytic

Platelets.—The platelets may be increased, normal, or decreased The fluctuations are great and the results reported by various observers are discordant hence changes in their number are of no value in the diagnosis of the condition

Bone Marrow Aspiration.—In some patients with Hodgkin s disease, without enlarged peripheral lymph nodes the diagnosis may be difficult As our experience with sternal marrow aspiration developed it was hoped that some diagnostic assistance might be secured from this procedure It has not been demonstrated however, that positive evidence of the disease can often be secured In any given case however it may be helpful by ruling out other conditions under consideration such as leukemia The sternal marrow in patients with Hodgkin s disease usually has a normal cellularity and myeloid erythroid ratio The myeloid cells may be slightly immature The mononuclears eosinophils histocytes and in some instances the lymphocytes are slightly increased in number Large granular cells with folded or indented nuclei may be observed Mature megakaryocytes are present in normal numbers

Diagnostically significant abnormalities were not demonstrated in the aspirated sternal marrow of 15 cases of Hodgkin s disease as reported by Cooper and Watkins *(106)* They did conclude however that such an examination is likely to prove of value in lymphosarcoma by the demonstrating of abnormal lymphocytic cells These authors present a comprehensive review of the literature Examination of the marrow obtained by sternal puncture from eight cases of Hodgkin s disease did not reveal abnormalities which were diagnostic according to Campion and Diggs *(107)*

Giant cells of the Reed Sternberg type have been found in the marrow of patients with Hodgkin s disease obtained with sternal aspiration by Cardozo and De Leeuw *(108)* but they emphasize the difficulty in differentiating such cells from megakaryocytes

The Gordon Test for Hodgkin s Disease.—In 1932 Gordon introduced the procedure which bears his name as a test for Hodgkin s disease He described a syndrome consisting of spastic paralysis incoordination and ataxia, retraction of the head convulsive seizures and weight loss which was produced in guinea pigs and rabbits following the intracerebral

injection of a broth suspension prepared from diseased lymph nodes from patients with Hodgkin's disease. It was suggested by Gordon that the effects were the results of the action of a virus but this has not been substantiated by other observers. Many workers have stressed its value as a diagnostic test in obscure cases although there is not a uniform opinion concerning its usefulness.

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It is my opinion that roentgen therapy should be regarded as a suppressive type of therapy and one which will not completely eradicate the

disease It should be applied to all areas in which it can be demonstrated by physical and roentgen examination that lymphoma tissue is present Lymph node enlargements should be treated as they appear Osseous involvement should receive local irradiation and pleural effusions should be treated by roentgen exposures over the anterior and posterior chest When systemic manifestations such as malaise fever anorexia and pruritis are present nitrogen mustard often produces gratifying results but it should be kept in mind that systemic involvement may be benefited by irradiation of the retroperitoneal glands The possibility of combining roentgen with nitrogen mustard therapy is promising and is discussed under the heading of the nitrogen mustards in the treatment of Hodgkin s disease

The indications for treatment are fever anemia and enlarged glands, which are exerting pressure on nerves of vital organs destructive bone lesions or in fact the apparent progression of any lesion which is thought to be producing symptoms The details of the dosage should be left to the roentgenologist who is experienced in such matters There are however two matters of caution which should be emphasized They are first in treating large lymphomatous masses especially involving the neck mediastinum or abdomen the initial treatment should be one of small dosage This is because the first effect of the therapy is to cause the tissues to swell and this may produce pressure symptoms or there may be rapid destruction of tissue which may produce a severe reaction by releasing a large amount of toxic products The second precaution which should be taken is with reference to the blood In the presence of a severe anemia or leukopenia treatment should be withheld until a number of blood transfusions have restored the red blood cell count and hemoglobin percentage to approximately normal

The Nitrogen Mustards —The earliest observations on the blood following mustard gas poisoning were made by Stewart (*110*) in 1918 when he reported on the leukocyte count in soldiers poisoned with this gas he observed an early leukocytosis followed by a leukopenia within three or four days Leukopenia was independently observed by Krumbhaar (*111*) who attributed this change to alterations in the bone marrow as a result of mustard gas poisoning The nitrogen mustards were introduced as a therapeutic measure in 1946 by Gilman and Philips (*112*) after the information had been suppressed as a security war measure for some time Rapid confirmations of their results were made by Jacobson and his associates (*113*) and by Goodman and his collaborators (*114*) More recently comprehensive articles dealing with clinical experience in the use of these preparations have appeared by Bauer and Erf (*115*) by Spurr and his associates (*116*) and by Karnofsky (*117*)

The introduction of these preparations has been a distinct advance in the treatment of Hodgkin s disease and allied disorders The most commonly used members of this group are methyl bis (betachloroethyl)

amine hydrochloride or HN 2 and E K 136 which is a double nitrogen mustard thought to have the same effect. Although the latter produces toxic effects less frequently they are more severe and prolonged when they do occur even toxic psychoses have been noted. The average dose of each preparation is 0.1 milligram per kilo of body weight given intravenously by injecting it into the rubber tubing of a free flowing intravenous saline infusion set to avoid irritation of the vein and the surrounding tissue. Such an injection is given every other day for four doses but in no instance should the total amount of the four doses exceed 24 milligrams. The mode of action is similar to the roentgen rays and at present is thought to be mainly by reaction with some nuclear component of the cell. These therapeutic agents have been reported as possessing the ability to arrest mitosis (*118*) to produce mutations in the lower forms of life (*119*) and to inhibit enzymes (*120 121*). These compounds have been employed with success in various types of lymphoid disorders especially in Hodgkin s disease lymphosarcoma follicular lymphoblastoma mycosis fungoides and reticulum cell sarcoma.

The indications for use of the nitrogen mustards in Hodgkin s disease and allied disorders are (1) the presence of the generalized form in which some of the involved areas are inaccessible to irradiation (2) in patients who no longer are benefited by roentgen therapy (3) in any patient in whom the white blood cell count is 3500 per cubic millimeter or higher (4) when further irradiation is precluded by the presence of threat of post irradiation changes and (5) to avoid post irradiation swelling in patients with involvement of the nervous system or obstructive mediastinal tumors.

The favorable effects of the nitrogen mustards may appear within a few days. There is prompt recession of the enlarged lymph nodes and spleen the fever itching cough chest pain and central nervous system symptoms often disappear and the general condition of the patient improves promptly. Mediastinal enlargements pleural effusions and ascites are more resistant. The effects are purely palliative as the duration of the improvement may be limited to as short a time as one month although in some patients the beneficial results may persist for several months to a year or longer. *There is clear evidence that an additional therapeutic effect may be attained by nitrogen mustard after the roentgen ray therapy is no longer effective*. Furthermore it is thought by some that x ray refractory patients may become resensitized to this agent by nitrogen mustard. There is also some suggestive evidence that the roentgen rays may resensitize a patient resistant to nitrogen mustard so that this preparation again becomes effective.

After an experience of five years Spurr and his associates (*116*) are of the opinion that roentgen therapy should be employed as long as it is effective in controlling local tumor masses and that nitrogen mustard

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age 25 has had enlarged glands in the neck for 20 years and 15 years ago he had a gland removed in our surgical outpatient department which was reported by our pathologist as typical of Hodgkin s disease During the years in which we have observed him he has received less than an average amount of roentgen therapy and except for moderately severe diabetes which he has had since childhood he was in good condition when last seen in 1949 At this time he was 25 years of age—20 years after he had developed the initial evidences of Hodgkin s disease and 15 years after it had been proven by biopsy

It is acknowledged that even in the carefully proven cases of Hodgkin s disease there is a wide variation in the length of life following the clinical onset of the disease There does not seem to be a satisfactory explanation for this other than the rather speculative one that in some patients the process is more virulent than in others or the patient has a greater resistance to it A careful study has failed to reveal any striking correlation between the length of survival and age sex, or the variations in the histology of the involved nodes Some of the cases that have pursued the most favorable course have been of the highly cellular type which have resembled sarcomatous Hodgkin s disease to a certain extent On the other hand those with a rapid course have had a considerable amount of fibrous tissue in the glands

The Effect of Irradiation —It has been pointed out by Slaughter and Craver (*13*) that 17 7 per cent of their 265 patients survived more than 10 years It is stated by Jackson (*86*) that nearly 30 per cent of the patients survive 5 years or longer and nearly 20 per cent 10 years or longer Goldman (*78*) found the average length of life from the onset of symptoms to be 32 months and the survival period following therapy to be 23 8 months He could find no correlation between the histopathological picture and the course of the disease The five year survival rate in his series was 10 per cent Gall and Mallory (*2*) report that 29 per cent with Hodgkin s lymphoma survived a five year period The latter authors subdivide their cases with great care and this may account for the longer duration of life reported in the Hodgkin s variety of lymphoma For example they observed an average survival of patients with Hodgkin s lymphoma of 3 2 years of Hodgkin s sarcoma of 0 9 year and of follicular lymphoma of five years Furthermore they report 29 per cent of their cases of Hodgkin s lymphoma lived for five years after the onset where 7 per cent of the Hodgkin s sarcoma and 53 per cent with follicular lymphoma have survived for a similar interval of time It is obviously of importance from the standpoint of prognosis therefore to distinguish between the various types of lymphoma

Our studies on the prognosis in Hodgkin s disease carried out on a series of 118 cases have been reported by Bethell Andrews Neligh and Meyers (*124*) The only significant type of treatment administered to

therapy be used as adjunct therapy in suppressing multicentric dissemination of the disease These observers do not believe that nitrogen mustard can be recommended as sole therapeutic agent in the lymphomas They state that patients who respond satisfactorily to roentgen therapy also respond well to treatment with nitrogen mustard The opinion is expressed by Bauer and Erf (*115*) that it is probably best to direct irradiation to local lesions and save nitrogen mustard for the generalized disease process With this conclusion I am in accord

Toxic Effects and Contraindications to Nitrogen Mustards—Nausea and vomiting follow treatment in almost every patient They may occur however, following some injections and not after others Rarely do they persist for longer than 8 hours except occasionally when S K 136 is given Gastro intestinal bleeding is observed rarely, and in a few instances a mild anemia and thrombocytopenia has developed The limiting factor to the treatment is the leukopenia which may become extreme within a few days falling to as low as 400 white blood cells per cubic millimeter It is not advisable to employ this form of treatment when the white blood cell count is below 3500 per cubic millimeter

ACTH and Cortisone—Recently Pearson and his associates (*122*) have reported the effect of ACTH and cortisone administered in four divided doses totaling 100 milligrams for the former and 200 milligrams daily for the latter, to a group of patients with lymphoid tumors In six patients there was a dramatic and progressive decrease in the size of the enlarged lymph nodes and the spleens, but in none of the patients was a complete clinical remission obtained These studies have not however established the efficacy of ACTH and cortisone as therapeutic agents in these conditions and the likelihood that they will produce only temporary benefit is great In a later publication (*133*) they state that such therapy produced slight shrinkage of lymph nodes and spleens in patients with Hodgkin s disease It is too early to form any definite conclusions concerning the therapeutic value of these therapeutic agents At present they do not appear to have great promise in the treatment of Hodgkin s disease It is possible however that with improved long acting and possibly more potent products future results will be more satisfactory

Prognosis—Experience indicates clearly that with a few possible exceptions Hodgkin s disease is a fatal disease which usually runs a spontaneous course of two to three years before terminating fatally

With roentgen therapy however in recent years it has been demonstrated that the average duration of life is three and one half years and about 30 per cent have a five year survival period With the more extensive use of the nitrogen mustards moreover the results in the future may even be better It is recognized that some patients have an amazingly long life after the disease is established which in some instances may extend for over 20 years One of our patients H M No 374728 now

a patient is treated with obliterative irradiation or surgical extirpation or preferably both a long survival rate may be attained Two cases reported by Baker and Mann (*125*) who were treated by surgical removal and subsequent irradiation have survived respectively 10 and 12 years and remained well up to the time of the authors report Slaughter and Craver (*13*) report on five patients whom they observed following surgical removal in an attempted cure These cases when considered with the two reported by Baker and Mann (*125*) show that the shortest survival period following treatment was five years and the survival periods in the cases observed by the latter authors were as follows 5 6 8 11 and 11 years This report again focuses attention on the possibility that in certain cases the combination of surgical extirpation and intensive irradiation may prolong life for a long period of time

Rarely is surgery now employed in the treatment of Hodgkin s disease although some still advocate this form of therapy It does not seem logical to anticipate worth while results from the local removal of a growth which probably in all cases affects many parts of the lymphatic system It must be admitted however that in the past some of the longest periods of survival have been in those patients in whom surgery has been performed In 1939 Jackson (*86*) who has had an extensive experience in the treatment of the disease says If however a case of Hodgkin s disease particularly of the lymphoma type be sharply limited to one area of the neck if the patient s general condition be good and if the peripheral blood picture sedimentation rate and basal metabolism be normal it would seem proper to attempt the complete removal of the involved tissue Such a procedure has been known to have resulted in cures of 15 to 20 years in duration but these cases are few and even after this lapse of time we cannot be entirely sure that the patient is free from the disease Still radical surgery is worth attempting in carefully selected cases

It should be kept in mind however that occasionally a patient with Hodgkin s disease survives for a long period without the aid of surgery in fact with little treatment of any kind

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them was x ray In 119 of these patients the duration of life *from the date of diagnosis which was usually within a few months of the onset of symptoms* was as follows *survival* of one year after date of diagnosis occurred in 59 7 per cent, after two years 42 0 per cent three years 29 4 per cent four years 25 2 per cent, five years 19 3 per cent, 10 years about 5 0 per cent

In surveying this group of patients for any manifestations which might be of prognostic value it was apparent that splenomegaly and leukopenia must be considered as signs of ominous significance Splenomegaly was present in 31 of our cases and of these 42 0 per cent survived for over one year 6 5 per cent for over two years and 3 2 for over three years

In comparison the group without splenomegaly 67 0 per cent survived for over one year 57 0 per cent for over two years and 40 5 for over three years

In our patients it was apparent that in those in whom the leukocyte count was persistently below 6000 per cubic millimeter not attributable to roentgen or nitrogen mustard therapy there was an unfavorable outlook Such a leukopenia is thought to be associated usually with an extensive bone marrow involvement

An extensive survey of the effect of the roentgen ray on the course of Hodgkin s disease has been made by Videbaek *(15)* A summary of his own results and those collected from various observers in the literature is given In his own 172 cases the average duration of the disease was three and one half years The survival rate is given calculated from the initial symptoms of 172 patients Twenty nine are still living Videbaek concludes that with roentgen treatment the average duration of the illness in his cases before a fatal termination was 3 3 years in males and 3 8 years in females Five years after the first symptom appeared 28 per cent of the patients were still alive and after 10 years only 3 per cent

One can offer some generalized statements in reference to the prognosis which may be helpful in any given case Those patients seem to do the best in whom the disease is localized to the upper portions of the cervical regions and who receive efficient roentgen ray therapy early in the course of the disease More unfavorable signs are those indicating an early skin involvement or that a primary lesion has occurred in bone or a viscus such as the thyroid intestine or the stomach Of unquestionable ominous import is the simultaneous presence of anemia and persistent fever either with a leukocytosis or leukopenia splenomegaly or the presence of leukopenia alone

The possibility of surgery is often discussed but rarely employed Slaughter and Craver *(13)* state that a certain type of case may be viewed with more optimism than heretofore They define such a case as one with only one accessible node group involved no deep adenopathy and no systemic symptoms as evidence of hidden disease When such

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CHAPTER XVIII

INFECTIOUS MONONUCLEOSIS

Synonyms.—Glandular fever acute benign lymphoblastosis acute lymphadenosis monocytic angina lymphocytic angina

Definition.—An acute self limiting rarely fatal generalized systemic infectious disease probably due to a filtrable virus characterized by fever lymphadenopathy the symptoms of an acute respiratory infection and other extremely diverse manifestations and the presence of atypical lymphocytes and sheep cell agglutinins (heterophile antibodies) in the circulating blood

History.—As no reference to an examination of the blood is made in the early descriptions of infectious mononucleosis it is not always possible to identify such conditions with certainty from the clinical descriptions alone. Hence it is difficult to be sure just who did first recognize the disease. It seems reasonable to suppose however that N Filatov in 1885 (*1*) was among the first to identify such a condition under the heading of Idiopathic Adenitis. It should be recognized however that H Gourichon (*2*) in his inaugural dissertation published in 1895 refers to the prior description of two other Russians Kisel and Rauchfuss who presented a case with the diagnosis of lymphadenitis at a meeting in St Petersburg a year before Filatov is said to have recognized the malady. Through the courtesy of Dr George H Houck Director of the Health Service of Stanford University I have been furnished with a translation of a portion of the first Russian edition of *Lectures of the Acute Infectious Diseases of Children* published in Russia by Nil Fyodorvich Filatov in 1885. In this he called attention to a disease which he states appears frequently in childhood and one in which no mention had been made in the medical literature. He gave it the name of Idiopathic Inflammation of the Lymphatic Glands. This he said occurred in children between the ages of 2 to 4 years and sometimes in children much older. He recognized that during the first seven to 10 days the disease runs the course of an acute adenitis with a febrile state and then subsides within two to three weeks. He described that only the glands of the neck became involved that they were firm to hard in consistency very painful when pressed and covered with a light reddish but not edematous skin

The classic presentation of Pfeiffer (*3*) is regarded correctly as one of the earliest and most complete descriptions of the condition. His paper entitled "Drusenfieber" appeared in 1889 at least six years before the

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patient from what they thought was lymphatic leukemia with a lymphocytosis of 97.5 per cent. This apparent cure was probably explained on the basis that the patient had infectious mononucleosis. According to Bernstein (*9*) Baetjer first mentioned the names infectious or infective mononucleosis in 1915, but Bernstein states it is more proper to consider that the terms were introduced by Evans and Sprunt in 1920 (*10*). In 1915 I was a student of Walter Baetjer in the course in Clinical Microscopy of which he had charge. After 29 years I have a distinct recollection of his lectures on leukemia but do not recall that he mentioned anything about infectious mononucleosis.

Another report, that of Richard C. Cabot's which appeared in 1913, should be mentioned, as in this he described four cases of which two and probably four had infectious mononucleosis. The title of his paper was "The Lymphocytosis of Infection" (*11*). R. Deussing in 1918 (*12*) described two cases in children with diphtheria in whom the peripheral blood showed a pronounced rise in the mononuclear cells.

In 1920 Evans and Sprunt (*10*) contributed an important paper on the disease with a good description of the abnormal cells which were encountered. They published a colored plate of the cells, and regarded as large lymphocytes all mononuclear cells seen that were not small lymphocytes or those of the large mononuclear transitional group, and hence included all pathological lymphocytes in this classification. The description by Longcope (*13*) of the cells and his conclusion that they were probably of lymphatic origin, along with his description of the microscopic appearance of an excised lymph node, did much to clarify the nature of the condition. The study of Downey and McKinley (*14*) with a careful description, including an excellent colored plate of the abnormal cells which they identified as atypical lymphocytes, is one of the most complete and accurate morphological studies which has been published.

Of great value from a diagnostic standpoint was the discovery by Paul and Bunnell in 1932 (*15*) that antibodies in high titer occurred in the sera of several patients with infectious mononucleosis which agglutinated sheep cells. It was later shown by Bunnell (*16*) that this reaction occurred in a great majority of patients with the disease and that it had sufficient specificity to be useful in the diagnosis of the malady. This reaction is based on the observation originally made by Forssman (*17*) that antibodies may react with an antigen which apparently had nothing to do with their development. These non-specific antibody-antigen reactions he designated as "heterogenetic," "heterophilic" or "heterophile."

Etiology.—*Age.*—There is a definite age limitation of importance from a diagnostic standpoint in the disease, for it almost always occurs in children and young adults. The oldest person with the disease observed by me has been 44 years of age, but it has occasionally been reported in old age. In general it should be said that it is rarely observed after the

report of Filatov was translated into German In this communication he states that it is his intention to record only the clinical picture in order that this may serve as a basis to which further observations could be added He includes in his description, high fever generalized aches and pains reddening of the throat, and painful lymph glands in the cervical region In the more seriously ill patients, in whom the active disease persists for eight to 10 days he states that the liver and spleen may be palpable, and an additional complaint is pain in the abdomen It is recorded that the course of the disease is always favorable and the glands never suppurate An amazing erroneous statement provided the disease is today what it was when he described it, is that "the glands which swell up in these cases *are only the glands of the neck especially of the nape the axillary and inguinal glands I have never found swollen*

The earliest study of infectious mononucleosis in the United States appears to have been made by J Park West (4) of Bellaire Ohio His observations were presented before the Section on Pediatrics of New York Academy of Medicine on November 12 1896 This observer had studied an epidemic of glandular fever as described by Pfeiffer which occurred in the practice of Dr F A Korell of Businessburg Ohio In this epidemic which was prevalent over portions of three years 96 cases of the disease appeared in 43 families In all instances, children were affected The oldest patient was 13 years of age and 56 of the 96 children were under five years of age This physician made a remarkably thorough study of the clinical manifestations of the condition but did not examine the blood in any instance Undoubtedly he expressed a correct opinion when he said that many cases called febricula and influenza will on close observation prove to be glandular fever, and that it occurs in a light form and as such is not often seen by physicians Another interesting statement which is not in accord with our present day ideas of the disease is that the most serious and frequent complication mentioned is acute nephritis ten cases of which have been recorded in the literature

The first article on the subject which appeared in England was written in 1897 and was by Dawson Williams with the title A Note on the Glandular Fever of Childhood (5)

There were no blood studies in the early cases of infectious mononucleosis Attention was focused on the blood with great interest in this condition by examples of what was thought to be recoveries from lymphatic leukemia One of the earliest of these was the case reported by Turk in 1907 (6) who was apparently surprised by the recovery of a young man from what he had considered to be lymphatic leukemia but undoubtedly the condition was infectious mononucleosis In 1909 Burns (7) noted the increase in the small mononuclear elements of the blood in a small epidemic in the wards of the Union Protestant Infirmary of Baltimore These observations were followed by other similar ones For example Ireland Baetjer and Ruhrah (8) described the recovery of a

nursing personnel in the hospitals throughout this country In the course of the routine blood study of all nurses admitted to the course in nurses training in 1942 in our hospital it was found that 53 per cent had the typical cells of infectious mononucleosis in their blood although rarely did any of them have symptoms The only explanation offered for this unusual situation is that they must have had the disease recently in a mild epidemic form with a persistence of the atypical cells in the blood

It is stated by Zarafonetis (22) that over 2000 cases were reported to the University of Michigan Student Health Service in the 20 year period between 1928 and 1948 Doubtless many more were not seen by the Health Service during this interval

Apparently the disease has a world wide distribution for it has been present when looked for in many countries It is of interest to note however that it is reported as occurring rarely in Negroes although it undoubtedly does occur According to Bernstein (9) not a single case of infectious mononucleosis in a Negro has appeared in the records of the Johns Hopkins Hospital and Kracke (23) considers the disease to be rare or possibly non existent in Negroes as he has never seen a case in the large Negro population of the Grady Hospital in Atlanta Georgia It may be that this can be accounted for by the fact that the condition is so commonly regarded as a mild respiratory infection unless careful and repeated blood studies are made Recently however Johnson (24) has reported two cases of infectious mononucleosis which occurred in Negro children The author states that as far as he knows these are the first serologically proved cases in the literature in this race He refers to one previous case in a male Negro reported by Longcope (13) Ray and Cecil (25) have also reported the condition in Negroes They observed three cases one of which was complicated by the presence of sickle cell anemia

Sex —Males are said to be some more commonly affected than females in a proportion of three to two but there is no known explanation for this

The Causative Agent of the Disease —The clinical picture of the disease indicates clearly that it is most likely due to a specific infectious agent Some have considered it to result from an abnormal reaction to a number of etiological factors but there is nothing which can be demonstrated in support of this theory Various types of bacteria spirochetes and a filtrable virus have been suspected of causing the condition but no conclusive evidence has been brought forward in support of these claims until recently Suggestive evidence is now available which indicates that a filtrable virus may be responsible for the disease but a recent report by Julianelle Bierbaum and Moore (26) does not confirm this

Of interest in this connection is the work reported by Wising in 1939 (27) He removed glands from three patients with infectious mononucleosis during the febrile stage and made an emulsion and later anti

age of 36 years and while the diagnosis of infectious mononucleosis in an older person may be correct it should always be viewed with suspicion

It has been estimated that about 80 per cent of all cases are in children under 13 years of age This perhaps places too much emphasis on the occurrence of the condition before young adult life in which it is common as anyone who has practiced medicine in a college community can readily testify Cases as young as seven months *(18)* and as old as 70 years *(19)* have been reported Bernstein *(9)* states that of his cases encountered among the population in and about a general hospital, as well as in private practice the youngest was six years the oldest 36 and 81 per cent were between the ages of 15 and 30 years

The immunity usually displayed by the older age group is well illustrated in the epidemic at the Lawrenceville school *(20)*, in which 112 of a total number of 500 student boys were sufficiently ill to be admitted to the infirmary whereas only one of 60 instructors was stricken

The only explanation for the apparent immunity of older persons is that possibly almost all have had the disease in childhood or young adult life which has rendered them immune to further attacks in a manner that many infectious diseases confer immunity in later years It is easily understood why persons may have the disease in an unrecognized form as it is often mild the glands may not be conspicuously enlarged and the complaints are not distinctive Undoubtedly more cases are over looked than are recognized correctly Many cases, especially in child hood are called the flu tonsillitis or an upper respiratory infection

An interesting point is made by Contratto *(21)* who after a large experience in treating patients in the health service of Harvard University states that never in his experience has a patient in an open ward contracted the disease from another patient Also he has never observed that one roommate has acquired the disease from another despite several days of exposure The experience is different from that which one meets with such highly contagious diseases as measles, German measles chicken pox and mumps Nevertheless one does see quite commonly more than one case in the same household especially among young children and the epidemic nature of the disease leaves no doubt as to its contagious nature

Incidence —Experience indicates that this is an exceedingly common disease and undoubtedly a very large majority of persons are afflicted with it during infancy childhood or early adult life Now that the specific Paul Bunnell test is available the incidence of the disease will probably be reported as greater because more cases will be recognized In Japan for instance there were a number of epidemic fevers of obscure origin which were finally identified as infectious mononucleosis by the Paul Bunnell test in 1937

Recognized cases have been exceedingly common in under graduate nurses at the University Hospital in Ann Arbor and this is true of all

obtained from patients with the disease and also whole blood were inoculated into the chorioallantoic membrane of chick embryos In a total of eight attempts to transmit the agent positive results were obtained in four A continuation of the reaction from four to 14 passages was obtained in about 50 per cent of the membranes but the agent finally died out Unsuccessful attempts were made to transmit the virus to 25 mice by intraperitoneal inoculation It was possible to produce a mononucleosis in rabbits by the injection of a suspension of ground chick membranes but it was not possible to obtain a positive heterophile reaction against sheep cells with serum from rabbits in which a mononucleosis had been produced by the agent Hence it appears as though a filtrable virus has been obtained from patients with this disease which can cause a mononucleosis in rabbits but it can hardly be conceded that the typical disease has been produced unless a positive sheep cell agglutinating factor is present in the blood of such an experimental animal Although these experiments are not conclusive they are highly suggestive and when considered with the clinical knowledge which is available suggest that a filtrable virus is the etiological agent

On the other hand rather extensive recent studies by Julianelle Bierbaum and Moore (26) fail to confirm these results as their attempts to transmit the disease to rabbits and monkeys mainly and to a lesser extent to white mice guinea pigs and man have failed In addition to the negative animal experiments these investigators were unable to transmit the condition to human volunteers by the intramuscular injection of material derived from an excised lymph node of a patient with the disease Although previous reports indicate that infectious mononucleosis may be due to a filtrable virus there is nothing in the experiments of these investigators to substantiate this belief There is apparently therefore a discrepancy between the results reported in the literature and these more recent negative results which indicate the need for further investigation of the subject

As a result of definite but transient evidence of the transmission of infectious mononucleosis to man in prior experiments (34) and encouraging reports by Wising (35) and by Sohier and his associates (36) further attempts were made by Evans (37) to transmit the disease to human subjects Sixteen human subjects were inoculated 10 with throat washings four with serum and two with stool preparations The routes used were principally nasal or oral intracutaneous subcutaneous or intragastric by tube Three of the 16 subjects showed uncertain signs of the disease but in no instance was there unequivocal evidence of successful transmission In not a single subject did all of the following occur 1 symptoms compatible with the usual course of the illness 2 objective physical signs especially lymphadenopathy 3 rise in lymphocyte count 4 the occurrence of atypical lymphocytes and 5 a rise in heterophile titer In no patient did the titer of this test increase The

gens from this material No organisms were recognized either microscopically or by cultures When these antigens were injected either intracerebrally or intracutaneously in monkeys fever enlarged glands and changes in the blood simulating infectious mononucleosis were observed An emulsion obtained from these glands and injected into three monkeys produced similar results During the course of these experiments one investigator accidentally inoculated himself and he had what Wising believed to be true infectious mononucleosis

Since the observation of Murray Webb and Swann (28) in 1926 that the organism of the genus Listerella (*Bacterium monocytogenes*) could produce mononucleosis in rabbits there has been speculation as to its possible etiologic relation to infectious mononucleosis in human beings In only a small proportion of the cases can such an organism be cultivated from the blood and spinal fluid and furthermore it has not been demonstrated that antibodies against organisms of this group develop in the serum of patients with infectious mononucleosis

In 1932 Nyfelt (29) isolated from the blood of human cases of infectious mononucleosis an organism which he called *B monocytogenes hominis* This was a small slow growing gram positive bacillus which causes a monocytosis when injected into dogs Since that time several other investigators have isolated the same organism from the blood or spinal fluid of patients with the disease and hence claims have been made that it is the etiological agent

Janeway and Dammin (30) undertook to study the etiologic importance of the genus Listerella group in infectious mononucleosis by determining if antibodies against them developed in the blood of patients with this disorder Their conclusion was that a slightly increased titer in the agglutination tests from the Listerella group appeared in the blood of patients with infectious mononucleosis as compared with the serum of the control groups There was no significant trend upward or downward however in the Listerella titer during the course of the disease or recovery from it From these observations it was concluded that the study did not suggest any definite etiologic relation between the Listerella organisms and infectious mononucleosis

Nettleship (31) has reviewed the literature in regard to the etiology of the disease and considers that the attempts to prove the relationship of various bacteria to the condition have all been unsuccessful In only one previous experimental study has an effort been made to demonstrate the etiologic relation of a bacterial free filtrate to the disease According to him the studies of van den Berghe and Liessens (32) and van den Berghe Liessens and Kovacs (33) indicate that the agent is a virus which is capable of producing the disease in monkeys Furthermore these investigators concluded that freezing appeared to increase the infectivity The studies made by Nettleship (31) dealing with this question may be summarized as follows sterile Berkefeld filtrates from the nasal washings

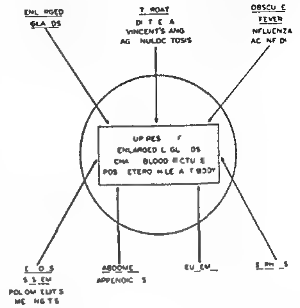

Fig. 67 — This diagram shows the diverse nature of the clinical picture in infectious mononucleosis along with certain features which are almost constantly present in all cases namely the manifestations of an upper respiratory infection the enlarged and tender glands the typical changes in the blood and the positive heterophile antibody reaction In some instances the enlarged glands may dominate the picture In others the symptoms referable to the throat may be of the greatest prominence when these are associated with a leukopenia especially in the early days of the illness the diagnosis of agranulocytosis may be suspected Certain other cases have as the presenting feature fever without obvious cause Occasionally the main complaints may be referable to the nervous system and the diagnosis of meningitis encephalitis or poliomyelitis may be made Abdominal pain may be the patient s chief complaint and lead to an appendectomy Not frequently the cells of infectious mononucleosis in the circulating blood are mistaken for lymphoblasts and the diagnosis of leukemia made erroneously In about 10 to 20 per cent of the cases the serological reactions for syphilis are positive and this sometimes leads to the incorrect diagnosis of syphilis To this chart should be added the clinical picture in which jaundice is prominent and in some epidemics an acute conjuctivitis is the outstanding complaint The diagram serves to emphasize the varied nature of the manifestations of this disease and stresses the fact that it may stimulate many other conditions (Sturgis courtesy *Clinics*)

rhage and one from postoperative hemorrhage In four other patients the ruptured spleen was removed and the patients recovered

The pathological findings reported by Custer and Smith (*41*) are presented in detail and merit the careful perusal of all who are interested in the disease This report is the most comprehensive study of this nature which has appeared in the literature to date In summary they found that the *gross* changes were almost entirely confined to enlargement of the lymphoid tissues especially the spleen Nasopharyngeal hyperplasia was constant and in one instance suggested tumor There were no other gross changes observed except (1) rather consistent enlargement of the liver (2) infrequent icterus and (3) occasional cutaneous rash The *histologic* changes were infiltration of the tissues and perivascular aggregates of normal and abnormal lymphocytes resembling the alterations observed in certain known virus diseases Reactions of this type involved all tissues except the bone marrow A pneumonia exudate in one

observer concluded that although a few subjects showed suggestive clinical or hematological signs of the disease the failure of a single subject to develop unmistakable evidence of the disease may be because the infectiousness of mononucleosis may have a low contagiousness under either natural or experimental circumstances

Pathology—As the disease is rarely fatal it has not been possible to make extensive pathological studies in a large group of uncomplicated cases Most of the information until recent years has been derived from biopsies (38) in which it was shown that the underlying lesions result from proliferation of the components of the lymph nodes with retention of the architectural relationships thus indicating the benign nature of the process

More recent observations (*39 40 41*) on necropsied cases have served to place the pathology of the condition on a *firm basis These studies* indicate that infectious mononucleosis is a generalized disease with an infiltration of abnormal lymphocytes in almost every organ of the body The patient reported by Ziegler (*39*) succumbed to the disease after an illness of between three and four weeks He concluded that the condition is an acute or subacute infectious disease of unknown cause in which the essential pathological findings are focal lesions in the various organs of the body especially the liver kidneys lymph glands and spleen This observer regards the disorder as a generalized infection with specific localization in one or more tissues or organs of the body In the spleen in addition to the atypical lymphocytes there are more primitive cells which might be classified as lymphoblasts or stem cells An infiltration of the liver and spleen with the cells of infectious mononucleosis" explains the enlargement of these organs Jaundice which occurs in infectious mononucleosis he attributes to an extensive focal hepatitis which appears to be a more plausible theory than assuming that it is due to the pressure of enlarged lymph glands on the common bile duct Although nerve tissue was not obtained for study Ziegler (39) states that one could readily imagine full sized mononuclear infiltration in the central nervous system and obstruction of the capillaries such as he demonstrated in the lung as a basis for the neurological manifestations of the disease

The most comprehensive study is that of Custer and Smith (*41*) who based their findings on nine necropsies and over 100 lymph node biopsies In addition further data were furnished by bone marrow biopsies, examinations of extirpated spleens tonsillar tissue and a number of liver and skin biopsies The cause of death in their nine patients with infectious mononucleosis was spontaneous rupture of the spleen in four Guillain Barre syndrome in two nasopharyngeal hemorrhage in one laryngeal edema in one, and airplane accident in one convalescent patient They report the cause of death in patients with the ruptured spleens as *follows* one was due to a blood transfusion reaction two from hemor

TABLE XL

GENERAL OBSERVATIONS

Symptom	Per Cent	Physical Signs	Per Cent
Headache	70	Fever	100
General Malaise	70	Enlarged Glands	100
Sore Throat	68	Postcervical	88
Tender Glands	60	Axillary	86
Backache	54	Subangular	64
Chilliness	44	Submaxillary	57
Anorexia	38	Inguinal	50
Coryza	36	Epitrochlear	32
Sweating	34	Submental	10
Weakness	32	Throat Injected	58
Cough	30	Enlarged Spleen	48
Stiff Neck	24	Membranous Angina	22
Abdominal Pain	16	Tenderness in Abdomen	4
Vomiting	12		

(Baldridge Rohner and Hansmann Courtesy *Archives of Internal Medicine*)

TABLE XL—The more important clinical manifestations of infectious mononucleosis are given in the above table. It should be noted that all patients are listed as having fever and enlarged glands which is true in my experience. These evidences of the disease however especially the lymphadenopathy may be absent in the first week of the patient's illness. Other *points to be kept in mind is that 24 per cent of the patients may complain of a stiff neck* and 16 per cent of abdominal pain. In some patients the latter may be the most severe symptom which may lead to a surgical operation on the basis that the patient has acute appendicitis. Furthermore it should be noted that almost one half of the patients have an enlarged spleen. In most instances this organ when enlarged is barely palpable. Gross enlargement of the *spleen should always suggest that the patient has some other condition than infectious mononucleosis*. The above table does not list all of the important symptoms as in epidemics of the disease there may be conjunctivitis and also jaundice as well as other symptoms.

tion of the physician and the true nature of the disease recognized in the case of the patient first observed *if other children or young adults in the household are examined* even though they have no complaints. In many instances it will be found that they have enlarged glands and give a history of experiencing symptoms so mild that they have been disregarded until questioned directly about them.

It should be mentioned that in the early stages of the disease the diagnosis is often puzzling and obscure because the *enlarged and tender glands the characteristic blood changes and the presence of heterophile antibodies in blood often do not appear until the end of the first week*.

The Fully Developed Clinical Picture.—Such a patient often has had fever for a period of 10 days to two weeks. This is usually of the remittent type and ordinarily does not exceed 101 to 102 degrees (F) for several days to a week and then is present to a lesser degree. I have observed patients however in whom the temperature remained continuously elevated in the vicinity of 103 to 104 degrees (F) for a period of a week or longer. There is a corresponding increase of the pulse rate and the respirations to a point which would be expected with the amount of fever.

case was almost exclusively of round cell type but in another the pneumonia was of the usual lobular type with a neutrophilic exudate A basis for the electrocardiographic changes was found in small myocardial infiltrates Of additional interest was the finding of periportal lymphoid collars in the liver which attained the proportions sometimes seen in leukemia and the presence of meningo encephalitis in four of the six brains examined It is their opinion that the majority of cells in the lymphocytic infiltrates about the vessels and in the connective tissues are metaplastic rather than inwandering and hence are formed *in situ* and arise from cells of the reticuloendothelial system

Symptoms and Signs —Comprehensive monographs dealing with all phases of infectious mononucleosis having extensive bibliographies have been published by Bernstein (9) and by Leibowitz (*41A*)

The clinical manifestations of this malady are exceedingly variable in nature and severity (*42 43*) There are a few fairly constant characteristics however which one should keep in mind They are (1) most cases have fever enlarged and tender glands and some symptoms of an acute respiratory infection (2) it almost always attacks children adolescents or young adults and (3) frequently an unduly extended period of convalescence varying from a few weeks to several months follows the acute phase of the illness

The incubation period probably varies from five to 11 days One encounters all degrees of severity of the disease There can be no question but what a walking type of infectious mononucleosis exists in which the patient has a certain amount of malaise a few enlarged glands with only slight swelling and tenderness and a mild febrile reaction which is overlooked On the other hand some patients with the disease may be so ill as to simulate a most serious infection and thus with the uncertainty regarding the diagnosis in the early stages of the disease may cause the attending physician considerable concern until the nature of the illness is established

Early Symptoms of the Disease —*The onset is almost always insidious* with malaise headache in addition to generalized and usually mild aches and pains fever chilly sensations but rarely an outspoken chill sore throat or other evidences of an upper respiratory infection At this particular stage of the illness the patient or even the physician not infrequently makes the diagnosis of flu which is one of convenience rather than accuracy In a few days to a week recovery may occur and the true nature of the disease remains unrecognized

It differs from the ordinary upper respiratory infection in that the *period of convalescence is often prolonged* and not infrequently the patient and the family are concerned about this state for which no obvious explanation is present and about which they had not been warned previously The frequency of the mild cases is often brought to the atten

A common finding is the presence of *enlarged and tender glands* which in my experience are to be found in almost every patient with the disease if a thorough and repeated search is made I would hesitate to make a diagnosis of this condition in the complete absence of enlarged peripheral lymph glands In rare instances however I have seen such cases in which no accessible glands have been enlarged despite a careful search The nodes are an almost constant feature of the disease according to Gendel and Cottrell (45) and in the 300 cases studied by Read and Helwig (43) they were present in 295 of the patients in 123 of the patients the glandular enlargement was limited to the cervical region In the study of a group of 72 patients with the disease in my department by Dr Abraham Becker a few years ago it was found that enlarged and tender glands were present in 94 per cent of the cases and that they constituted the presenting symptom in 28 per cent Those in the cervical region were involved in all cases except one in whom it was restricted to the axillary region Of the four patients without lymphadenopathy one had abdominal pain with an hepatomegaly and splenomegaly another had swelling of the eyelids and two had tonsillitis as the outstanding manifestations

It has been stated by Contratto (21) contrary to the experience of most observers that the lymphadenopathy is not infrequently absent It is surprising to me to learn that 17 per cent of his patients had no enlargement of the peripheral nodes at any time during the illness although the clinical course the changes in the circulating blood and the heterophile reaction indicated that the diagnosis of infectious mononucleosis was correct Furthermore this same observer states that the lymphadenopathy when present is not likely in a great majority of cases to appear early in the disease Only about 10 per cent of his patients had enlarged lymph nodes when first observed Many acquired enlarged superficial lymph nodes in several days or a week after the onset of the illness but a moderate number had no lymphadenopathy until the other symptoms had abated and they were well on their way to recovery Usually the lymphadenopathy is eventually demonstrable in the patients I have seen but in some its appearance has been delayed until the disease has been present for a week or more and then the enlargement has not always been pronounced In other words in almost all instances repeated examinations will ultimately disclose glandular enlargement whereas one or more examinations in the early stages of the disease may fail to demonstrate it Furthermore glandular enlargement in the axillae especially if it is done hurriedly or superficially may fail to detect sizable glandular enlargement because sometimes the palpating finger will push the gland higher into the axilla instead of fixing it against the chest wall where it can be felt

The enlarged glands are most frequently encountered in the posterior cervical chain but usually there is generalized enlargement They

Never have I observed *definite rigors* although it is not uncommon to have *chilly sensations* at the onset A patient seen by Rinzler and Hertz (*44*) had outspoken chills, however and proved to be a difficult diagnostic problem The patient was a white male of 25 years who was seen on the sixth day of his illness complaining of malaise fever and swelling of the glands of the right side of his neck On the eleventh day the heterophile antibody reaction was negative About this time the main clinical manifestation was severe shaking chills followed by a temperature rise to *almost 105 degrees (F)* The possibility of typhoid fever malaria acute leukemia or acute Hodgkin s disease was considered On the fifteenth

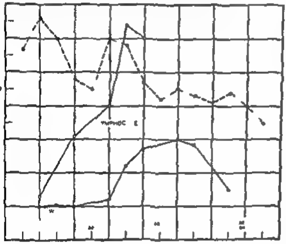

Fig 68 —Patient with infectious mononucleosis who presented a puzzling diagnostic problem when first seen The body temperature varied from 102 to 104 degrees (F) shortly after admission the spleen was palpable no lymph glands were enlarged or tender and the total white blood cell count was 5000 per cubic millimeter with 22 per cent normal lymphocytes The patients only complaints were those incident to fever The diagnosis of typhoid fever was entertained It was not until the fifth day in the hospital and the seventh day of the illness that the diagnosis of infectious mononucleosis was considered *seriously* At this time a few small tender glands in the posterior triangles of the neck were *felt the heterophile* antibody reaction was 2 plus positive and the lymphocytes had increased to 41 per cent a few were of the "infectious mononucleosis" type Later the diagnosis became obvious with an increase of the lymphocytes to 75 per cent almost all of them being of the type seen in *infectious mononucleosis* and the total white blood cell count rose to 15 000 per cubic millimeter

day of the illness the heterophile antibody reaction was positive in a *dilution of 1 64 and 18 per cent of the white blood cells in the circulating* blood were the typical pathological lymphocytes of the disease Recovery was uneventful

In practically every instance there are *symptoms referable to the nose and throat* which vary in intensity from a mild rhinitis or pharyngitis to *ulcerative follicular or membranous tonsillitis or Vincent s angina* About three fourths of the patients have some objective evidence of such an infection the most frequent being injection of the pharynx hypertrophy of the lymphoid tissue and occasionally membrane formation When the disease is not ushered in with the symptoms of sore throat the initial manifestations are those of influenza or an ordinary cold

pendectomy has been performed occasionally in such patients on the basis of a mistaken diagnosis

The cause of the abdominal pain is not clear. The possibility of it being due to swelling of lymph glands in the mesenteric region or the spleen must be considered and enlarged abdominal glands have been observed at operation. It is possible that many cases of so-called mesentery lymphadenitis are really a part of the syndrome of infectious mononucleosis. Lesions have been found in the lymphoid tissue of the appendix which are identical with those present in the glands of infectious mononucleosis but they are not a constant finding in these cases

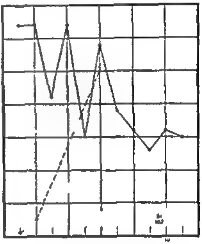

Fig 69 —Patient with infectious mononucleosis in whom the presenting symptoms were severe generalized abdominal pain and fever. The diagnosis of acute appendicitis had been made by the referring physician and the patient admitted to the surgical service. The presence of a generalized lymph gland enlargement however resulted in a medical consultation and the diagnosis of infectious mononucleosis was tentatively made. It was not until a few days later however that the white blood cell count increased the characteristic cells of infectious mononucleosis appeared in the circulating blood and the heterophile antibody reaction became positive

Certainly it is wise for the physician to keep in mind the possibility of infectious mononucleosis in all children and young adults as a possible explanation of acute abdominal pain. In such cases the enlarged peripheral lymph glands the changes in the blood and the heterophile antibody reaction may be of help in recognizing the true nature of the condition but it must be remembered that the pain may be present for several days to a week before these changes appear in some cases

Neurological Manifestations—Headache of a variable intensity is a common complaint in infectious mononucleosis occurring in almost three fourths of the patients. In some instances it is more than an annoying type which may be present in almost any infection but is severe and persistent and constitutes the main presenting symptom. In about one quarter of the patients who have the disease there is some degree of stiffness of the neck although it is usually minor in degree. Occasionally the neurological manifestations dominate the clinical picture with severe headache evidences of meningeal irritation such as a stiff neck and a positive Kernig's sign and blurring of vision. These changes direct at

are usually slightly tender and vary from the size of a pea to a 25 cent piece. Characteristically they are non adherent, firm and never in my experience have they suppurated although this complication has been reported in rare instances. In my opinion this is due as it is occasionally in patients with lymphatic leukemia to secondary infection, in some instances with the tubercle bacillus.

A *cutaneous rash occurred in 18 5* per cent of a group of patients seen by Templeton and Sutherland (*46*) a great majority of which were of a *fine macular character with occasionally a certain papular element* present. They assert that it was *practically indistinguishable from German measles*. The trunk *was most frequently involved, with the face running* a close second. The remaining patients with an eruption had multiform lesions or slight erythema of the face or abdomen. There was slight if any itching. The condition appeared at any time from the third to the twentieth day persisted from three to seven days, and faded without desquamation. They considered the possibility that the eruption may have been due to drugs such as barbiturates but concluded that it is probably directly associated with the disease.

Ocular Involvement.—It has been stated that ocular symptoms are not common but they do occur more frequently than one is led to believe, and when present are often prominent. In the early stages there may be pain *in or back of the eyes which may diminish as the disease progresses* but leaves the patient with puffy eyelids. In a group of 21 cases reported by Ash and Arbogast (*47*) *a conjunctivitis was present* in 10 of the patients. I have observed such a condition in patients with the disease but it has not been common or severe.

Of great diagnostic importance is the observation by Ashworth and Motto (*48*) and by Blaustein and Caccavo (*48*) that in rare instances the disorder may be complicated by bilateral papilloretinal edema. Until the former report appeared the transient ocular condition had not been recorded in the absence of a clinical picture of meningitis or encephalitis. A similar ocular change was observed by Blaustein and Caccavo (49) in a 23 year old man who had suffered a blow on the head with a derrick hook one month previously and subsequently complained of severe headache. *Furthermore he had been exposed to an open* case of tuberculosis. The possible diagnoses of subdural hemorrhage and tuberculous meningitis were entertained but the subsequent history and laboratory data confirmed the diagnosis of infectious mononucleosis.

Abdominal Complaints Which Suggest the Need of Surgical Intervention.—Persistent and sometimes severe abdominal pain is present in 16 to 18 per cent of all patients with the disease and nausea and vomiting in about 12 per cent. *These complaints alone are enough to suggest* that the patient may be suffering from an attack of acute appendicitis. As the lymphadenopathy the blood changes and the heterophile antibody reaction may be delayed for a week or more it is not surprising that ap-

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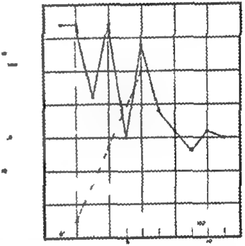

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of this disease in the neighborhood The headache persisted unabated for almost a week The neck was stiff and a positive Kernig's sign was present The spinal fluid showed no changes When first examined a careful search for enlarged glands was made the blood was examined for cells of infectious mononucleosis and none found and the heterophile antibody reaction was negative These examinations were made thoroughly because the diagnosis of infectious mononucleosis with meningeal symptoms was under consideration About one week after the onset small tender glands appeared in the neck the typical cells of infectious mononucleosis were found in the blood and the heterophile antibody reaction became positive in a dilution of 1–64

Although the neurological manifestation when present usually denotes a meningeal type of reaction in some instances there may be evidence of more serious involvement with speech difficulty sluggishness transient paralysis ptosis and mental confusion all of which may suggest an encephalitis According to Lassen and Thomsen (52) the process may localize selectively in the respiratory center and there produce paralysis with a fatal termination A case of infectious mononucleosis is reported by Field (53) in which there was severe central nervous system involvement as shown by transitory paralysis right homonymous hemianopsia and a great increase in spinal fluid protein Subsequently the patient made a complete recovery A fatal case of infectious mononucleosis is presented by Dolgopol and Husson (54) in which the early neurological symptom was diplopia Neurological manifestations which developed later were those of a bulbar lesion with respiratory paralysis and lower paraplegia This appeared before the lymphadenopathy and splenomegaly The patient succumbed after an illness which had a total duration of nine days Necropsy showed degenerative changes in the nuclei of the third and fourth cranial nerves and in the inferior reticular nucleus of the medulla and some degeneration of the Purkinje cells of the cerebellum In the spinal cord hemorrhages were present in the gray matter chiefly in the posterior horns but in the lumbar region the hemorrhages had extended to the anterior horns as well

An unusual complication of infectious mononucleosis *infectious neuronitis* (*the Guillain Barre syndrome*) previously not reported has been observed by Hiller and Fox (55) This patient was a 17 year old girl who obviously had infectious mononucleosis About three weeks after the onset she developed a lower extremity motor paralysis of an ascending character with an accompanying involvement of the facial nerve and an acellular hyperalbuminosis of the spinal fluid According to the authors most of the cases of the Guillain Barre syndrome follow as sequellae to nasopharyngeal pharyngeal or upper respiratory infections It is always a likelihood however in the opinion of these authors that an infectious neuronitis may complicate many other virus infections They

tention to the nervous system and in some cases, the erroneous diagnosis of benign lymphocytic meningitis encephalitis or abortive poliomyelitis has been made

A comprehensive review of the literature dealing with the involvement of the nervous system in infectious *mononucleosis* and the report of a case with meningo encephalitis is given by Bernstein and Wolff (*50*) They state that to the time of publication of their article there had been 28 reports dealing with this topic, including 46 patients Of these however, only 34 cases fulfilled the requirements for involvement of the nervous system This would indicate an incidence of less than 1 per cent Serious meningitis meningitis encephalitis meningo encephalitis polyneuritis and peripheral neuropathy have been observed The most common neurological complication was meningitis alone, or complicated with an encephalitis or polyneuritis It is their opinion that the nervous system is invaded directly by the unknown agent causing the disease The *changes in the spinal fluid* consisted of an increase in the number of lymphocytes with or without an increase in protein Apparently changes in the spinal fluid may occur not infrequently in patients with this disease without associated sensory motor or mental defects being observed In the opinion of these authors, the *prognosis* is excellent as 85 per cent of the patients made a complete recovery Since in these cases, the systemic signs of infectious mononucleosis may be minimal, and the clinical picture of involvement of the nervous system is indistinguishable from that caused by many other agents the heterophile antibody test should be done on all patients with evidence of involvement of the nervous system in which the cause of the disorder is not clear

It is emphasized by Bercel (*51*) that patients with infectious mononucleosis who complain of headache dizziness and somnolence may have serious brain damage In 31 such patients referred to him for neurologic examination serial electroencephalograms showed evidence of encephalopathy in five Two of the five showed changes in the electroencephalograms and subsequently clinical evidence of post encephalitic epilepsy While complications may occur occasionally it must be exceedingly uncommon when one considers the high incidence of infectious mononucleosis and the rarity of evidence suggesting serious injury to the brain

It should be noted therefore that the neurological involvement may occur before the other signs of infectious mononucleosis are present Hence for a week or more the patients complaints may be entirely referable to the nervous system and the lymphadenopathy the positive Paul Bunnell test and the atypical lymphocytes in the circulating blood appear at a later date In one patient a girl of 16 years who was under my observation with a chief complaint of an intense headache it was feared that she had poliomyelitis because at this time there was an epidemic

A comprehensive discussion of jaundice in infectious mononucleosis is given by de Vries (63) in which he recognizes three different clinical types one in which jaundice is the first symptom followed subsequently by glandular enlargement a second form in the jaundice appears along with the glandular enlargement a third variety in which jaundice with or without fever is the only symptom

In a comprehensive review of the literature and a study of their own 24 patients with infectious mononucleosis it was concluded by Jordan and Albright (60) that hepatitis occurs in a majority of patients with the disorder It is their opinion that the hepatitis which frequently occurs is a mild non icteric usually transient process as demonstrated by liver function tests On the other hand jaundice is sometimes prolonged and hepatic involvement may be more than a transient affair They found elevated cephalin cholesterol flocculation and thymol turbidity values in 73 and 83 per cent of the patients respectively Abnormal bromsulfalein excretion was found in 71 per cent and the alkaline phosphatase was elevated in 38 per cent of those tested The largest number of changes in the liver function test were observed in the second and third weeks of the disease The most persistent abnormalities were the altered cephalin flocculation and thymol turbidity reactions which lasted more than two months in one fourth of the patients In general these observers concluded that serial studies of the state of the liver in patients with infectious mononucleosis indicated that approximately two thirds to three fourths of patients have an associated hepatitis

In studying 83 patients with infectious mononucleosis it was found by Brown Sims White and Clifford (64) that positive tests were present in 75 or about 89 per cent of all the tests employed the cephalin cholesterol flocculation was positive most frequently a value of +++ was obtained in 38 of 39 patients who had a series of tests It is also the opinion of Evans (65) that the cephalin cholesterol flocculation reaction is a more sensitive indicator of this form of hepatic dysfunction than the thymol turbidity test and may be used in differentiating such cases from uncomplicated upper respiratory infections It persisted for an average of 30 days It is their conclusion that when infectious hepatitis of viral origin can be eliminated with reasonably certainty the cephalin cholesterol flocculation test is a valuable aid in the early diagnosis of infectious mononucleosis They are in accord with the conclusions of other observers namely that true hepatitis occurs in a significant number of patients with infectious mononucleosis Furthermore it is their opinion that accurate differentiation between this disorder and infectious hepatitis with or without jaundice is impossible in occasional cases

The studies of Bennett and his associates (66) is in agreement with those of other observers namely that hepatitis is a frequent and probably regular manifestation of infectious mononucleosis Jaundice occurred

suggest that in the future all cases of the Guillain Barre syndrome have a heterophile antibody test The Guillain Barre syndrome in a case of infectious mononucleosis is reported by Butt (*56*) in which rapid improvement followed the addition of 2 3 dimercaptopropanol (BAL)

The case of a 25 year old married male is described by Raymond and Williams (57) with infectious mononucleosis who developed a *toxic psychosis resembling schizophrenia*, although the possibility was considered that the patient s symptoms might be explained on the basis of an actual schizophrenia precipitated by the disease

Jaundice and Liver Involvement, Including Cirrhosis in Infectious Mononucleosis—Jaundice in association with bona fide cases of infectious mononucleosis occurs more commonly than is usually thought The literature on hepatic dysfunction in patients with infectious mononucleosis is reviewed by Peterson (*58*) by Liebowitz and Brody (*59*), and by Jordan and Albright (*60*) Icterus was observed in 10 per cent of the patients in a series studied by Contratto (*21*) and in about the same incidence by Abrams (*61*) In most cases it was not noted until four to five days after the onset but in some instances it did not become apparent for 10 days to two weeks It is stated by Contratto (*21*) that the jaundice associated with infectious mononucleosis has the same symptoms physical signs and clinical course as acute catarrhal jaundice The presence of jaundice nausea vomiting and fever in a young person however may be explained erroneously on the basis of acute hepatitis and the fact that the patient has infectious mononucleosis be overlooked But in some such cases indisputable evidence of infectious mononucleosis has been found The development of the icterus before the characteristic manifestations of infectious mononucleosis appear such as lymphadenopathy or splenomegaly quite naturally would suggest the diagnosis of acute hepatitis

The depth of the icterus is usually slight Some believe that if the urine was tested more frequently for bile that evidence of latent jaundice would be detected in a greater number of cases Occasionally the icterus may be intense as indicated by a serum bilirubin of 23 3 milligrams per 100 cc of blood and an icterus index of 150 units (*62*) A case is reported by Abrams (*61*) in a 30 year old man in whom the illness lasted for 13 weeks and the jaundice persisted for a total of 11 weeks The jaundice was intense as indicated by an icterus index of 210 and a direct Van den Bergh reaction with a bilirubin of 20 milligrams per 100 cc

The cause of the icterus has been in dispute in the past but the recent report of Ziegler (*39*) has clarified the situation It had previously been believed that it was an obstructive jaundice due to pressure of enlarged glands on the common duct at the hilum of the liver It has been shown by Ziegler however that the cause is an extensive focal hepatitis

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rarely in their patients however despite the fact that 90 2 per cent of them had one or more abnormal liver tests They concluded from evidence obtained by punch biopsies, and necropsy observations on several patients who died from spontaneous rupture of the spleen that the deranged liver function is the result of hepatocellular involvement similar to that seen in infectious hepatitis and is not due to extrahepatic obstruction by enlarged glands

It was found by Peterson (58) that 55 per cent of a series of forty patients with infectious mononucleosis showed moderate to severe hepatic functional *involvement or hepatitis as indicated by changes in a battery* of liver function tests This observer concurs in the belief that the hepatic damage is on the basis of hepatocellular and cholangiolar liver injury

The case of a 24 year old man is reported by Leibowitz and Brody (59) in whom cirrhosis of the liver developed following infectious mononucleosis These observers believe that the occurrence of permanent liver damage is rare following this disorder even less common than in infectious hepatitis In both diseases however they consider that the existence of primary liver damage is now proven and the hepatic injury is similar

Splenomegaly and Splenic Rupture—The spleen is palpable in approximately one half of the cases In my experience it is usually slightly tender and usually does not extend more than two finger breadths below the left costal margin The presence of a *grossly enlarged spleen* should cast considerable *doubt on the diagnosis and cause one to consider the possi*bility of a leukemia or some type of lymphoblastoma The spleen was palpable in 34 of our 72 cases and the liver in eight The latter organ never shows more than a slight or moderate increase in size *A palpable* spleen was present in 91 of 196 patients or slightly over one half of the patients observed by Contratto (21) Of his 91 patients the spleen was barely felt in 67 and easily palpable in 15 in nine instances it was enlarged two finger breadths below the left coastal margin He found that the spleen usually recedes along with the lymph nodes but in some of his patients it was still palpable at the end of the year after the acute illness had subsided

It is of interest that rupture of the spleen may occur spontaneously in these patients or from relatively mild trauma When the great frequency of the disease is considered along with the relatively few instances of ruptured spleen it must be regarded as an exceedingly rare complication Since the first description of rupture of the spleen in this disease by King (67) a total of 12 cases have been reported with a mortality of 54 *per cent* according to Cendel and Cottrell (45) who reviewed the literature on this topic

Cardiac Complications—Ordinarily one is not concerned with the cardiac status in patients with *infectious mononucleosis* as the disease is

usually mild in nature and it almost always affects the younger age group. It has been shown in recent years, however, that in rare instances the heart does not escape involvement. In 1946 Evans and Graybiel (*68*) reported that during the course of an epidemic in which upwards of 100 cases were observed, it was noted that the heart was affected in four. In these patients there were low or inverted T waves which were interpreted to indicate pericardial involvement, and in one patient a friction rub was heard; in another there was slight cardiac enlargement. These data were taken to indicate that the cardiac involvement was largely pericardial. The literature dealing with the subject is reviewed by Jaffe, Field, and Master (*69*). They also report studies on 22 cases of infectious mononucleosis in which pronounced T wave changes were present in nine cases or 41 per cent. In addition to the T wave changes there was prolongation of the P-R interval in two of the cases. It is their conclusion that the electrocardiographic changes in this disorder are nonspecific and resemble those observed in numerous other acute infectious diseases.

The Blood Platelets, Thrombocytopenic Purpura, and Abnormal Tendency to Bleed.—Ordinarily the blood platelets are normal in number and there is no hemorrhagic tendency in this disease. If there is a reduction in platelets with a thrombocytopenic purpura, suspicion should be aroused that it is due to some other etiological agent. It has been demonstrated rarely in recent years, however, that a thrombocytopenic purpura may occur in association with infectious mononucleosis. Probably the first case in which this complication was mentioned was reported by Minot (*70*). A complete review of the literature is given by Angle and Alt (*71*). They also observed a case and state that six others have been reported in the literature. They made serial blood platelets counts on seven consecutive cases with infectious mononucleosis in whom no hemorrhagic manifestations were present. It was their conclusion that a slight depression in the platelet count occurred early in the illness followed by a thrombocytosis and a subsequent return to normal. In their opinion hypersplenism should be considered as a possible cause for the thrombocytopenia.

A short time ago an 18-year-old female was admitted to the Simpson Memorial Institute of the University of Michigan. A clerk in a department store, she was well until two weeks before admission when she developed a minimal sore throat without other associated symptoms. About three days later she felt weak, slightly dizzy, and noticed the appearance of numerous small red spots over her lower extremities after she had been standing all day. The purpuric areas increased, persistent epistaxsis developed, and she vomited about 250 cc. of blood material the morning of admission. When seen at the hospital the patient appeared to be in a condition of shock with a systolic blood pressure of 80 mm. Hg and a diastolic which could not be determined. There were numerous

petechiae over the body no lymph nodes were palpable but the spleen edge could be felt 4 centimeters below the costal margin The hemoglobin was 7 5 grams per 100 cc the white blood cell count 26 650 per cubic millimeter with 74 per cent large lymphocytes, typical of the cells seen in infectious mononucleosis the reticulocytes were slightly increased and the platelets were almost absent from the circulating blood The prothrombin time was 52 per cent of normal The heterophile antibody reaction was positive in a dilution of 1-64 A blood transfusion of 1000 cc was given immediately and the patient showed signs of improvement promptly and was discharged from the hospital in one week In the subsequent four months period of observation she remained in excellent health

Since the summary of Angle and Alt (*71*) two other cases have been reported by Kutzer and Allen (*72*)

All cases in which it was established that the patient had previously been in good health and then developed thrombocytopenic purpura as a complication of infectious mononucleosis made good recoveries with a complete disappearance of all purpuric manifestations Patients have been reported however in whom the infectious mononucleosis probably aggravated a previously existing hemorrhagic diathiasis and in whom the hemorrhagic tendency persisted after all evidence of infectious mononucleosis had disappeared (*9, 73*)

An abnormal tendency to bleed as previously stated does not occur frequently in patients with infectious mononucleosis but it may be present and is of importance for at least two reasons 1 It may confuse the condition with acute leukemia and 2 the presence of bleeding may divert attention from the diagnosis of infectious mononucleosis In a study of 300 cases Read and Helwig (*43*) state that four patients of the group had an admission diagnosis of epistaxsis and in six it was a complaint on admission In the same group petechiae were present in nine patients which involved the oral cavity of four as well as being generalized

In 1923 McKinlay and Downey (*74*) observed hemorrhage into the mucous membranes in two of his nine cases and in his opinion they differed only in their moderate degree from those observed in leukemia there is no record that platelet counts were done Fatal nasopharngeal hemorrhage is reported by Custer and Smith (*41*) rectal hemorrhage with the loss of over a pint of blood for which no cause could be found on the basis of thrombopenia or by sigmoidoscopic or roentgen examinations was observed by Eckstein and Peeney (*75*) hemoptysis is reported by Sears (*76*) The case of an 18 year old girl who voided frankly bloody urine was observed by Thompson and Pitt (*77*) the blood platelets were said to be normal on stained blood film

Changes in the Blood —The usual characteristic changes in the blood are the presence of circulating abnormal lymphocytes in number exceed

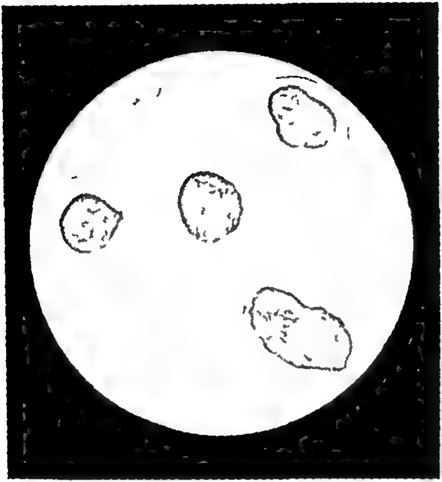

PLATE IX *Infectious Mononucleosis*—The leukocyte count was 18 000 per cubic millimeter with 75 per cent of the cells atypical lymphocyte variants of the type illustrated. The three upper cells possess nuclei with relatively dense chromatin like that of mature lymphocytes but there also may be observed small clear spaces or fenestrations which are quite characteristic of this disease. The cell in the lower portion of the field is a younger or prolymphocytic form with a large light staining nucleus. All of the cells possess abundant foamy cytoplasm of irregular outline readily indented by adjacent erythrocytes and characterized by variable and uneven basophilic staining properties. Wright's stain. Magnification 960

ing 50 per cent and a white blood cell count between 10 000 and 20 000 per cubic millimeter The red blood cells hemoglobin and platelets of the circulating blood are almost always normal Exceptions to this do occur however for in rare instances which have been discussed previously (see page 961) an anemia or thrombocytopenic purpura may develop

The Leukocytes—In about two thirds of the cases, there is an increase in the total number of white blood cells to between 12 000 and 16 000 per cubic millimeter at some time during the course of the disease During the first week of the illness a leukopenia is frequently present with a total leukocyte count which may be as low as 1500 to 2500 per cubic millimeter In about one third of the cases the white blood cell count does not rise above 10 000 per cubic millimeter at any time Occasionally the total count may increase to above 40 000 per cubic millimeter but this is unusual

The Characteristic Cells of Infectious Mononucleosis—The most distinctive cells in this condition are abnormal lymphocytes which can be readily identified by an experienced hematologist To one who is less experienced these cells may be regarded as lymphoblasts or even be passed over as entirely normal

The cells vary in size from that of a small lymphocyte to a normal monocyte They have an indented lobulated or kidney shaped nucleus which has a chromatin arrangement similar to that seen in a mature lymphocyte The cytoplasm is basophilic in varying degrees resembling to some extent that of plasma cells With Wright s stain this is often sky blue in color and has a perinuclear clear zone One of the outstanding features of the cells is the presence of exceedingly minute vacuoles in the cytoplasm which give a highly distinctive foamy appearance This latter change usually stamps such cells as those of infectious mononucleosis With very few exceptions when the disease is fully developed they comprise 50 per cent or more of all white cells present in the circulating blood In over three fourths of the patients they make up between 60 and 90 per cent

These cells may disappear within the course of a few weeks but in some instances they have been known to persist in the circulating blood for an astonishingly long period of time For example Farley (78) cites the almost unbelievable case of a patient who had 60 per cent of mononuclear cells six years after the acute illness and even after 10½ years these characteristic cells were present This is a most unusual instance but it is not so rare to have such cells persist in the blood for three to six months

The typical blood findings in the disease is considered by Contratto (21) to be a reduction in the percentage of neutrophil cells to below 40 and the presence of a large number of so called atypical lymphocytes For the most part in his patients the initial white count was normal or

only slightly elevated, but in one instance it reached a level of 31 000 per cubic millimeter and in seven instances in the 196 patients it was above 25,000 per cubic millimeter He found that the leukocyte count is highest from the fifth to the twentieth day of the illness and the reduction in the percentage of polymorphonuclear cells also occurs during this period The characteristic changes ordinarily persisted for a period of about two weeks sometimes shorter In rare instances Contratto found atypical lymphocytes present in the circulating blood two months after the acute symptoms had subsided

In a study of 25 cases of infectious mononucleosis by Litwins and Leibowitz *(79)*, the typical lymphocytes characteristic of the disease were found in every case They appeared as early as the first day of the illness in one case and as late as the 25th day in another They observed these cells to persist for as long as 286 days The percentage of lymphocytes in each one of the 25 cases varied from 40 to 89, with all but one being above 60 per cent The average maximum was 72 6 per cent and the average day of the illness when the abnormal lymphocytes were first detected was 9 8 but the circumstances concerning the day on which the blood was first obtained made the authors believe that the truer average was lower than 9 8 days which would be in accord with my experience These observers believe that although the abnormal lymphocyte is characteristic of infectious mononucleosis it is *not pathognomonic for this disease* From their own experience and a review of the literature they conclude that similar cells may be present in the blood of patients with virus hepatitis virus pneumonia herpes zoster herpes simplex and roseola infantum They also state that this type of cell has been reported as occurring in the blood of patients with rubeola rubella influenza type B upper respiratory infection undulant fever and rickettsial pox One would think however that the diagnosis in some of these disorders might be questioned and that the patient may have been suffering from true infectious mononucleosis

Red Blood Cells and Hemoglobin—Almost always the red blood cells and hemoglobin content of the circulating blood are normal Anemia may occur occasionally however due to two complicating factors First and most common it may develop in association with some other unrelated disease as an iron deficiency anemia which is not uncommon in children and young adult females Second hemolytic anemia may occur in exceedingly rare instances possibly due to hypersplenism A case has been reported by Appleman and Morrison (80) Read and Helwig (43) observed six cases in 300 patients with the disease and another requiring splenectomy is reported by Wilson War and Gray *(81)* More recently Small and Hadley (82) observed a patient with infectious mononucleosis who developed a severe acute hemolytic anemia with a red blood cell count of 1 75 millions per cubic millimeter many lymphocytes character

istic of infectious mononucleosis and a heterophile agglutination test positive in a dilution of 1 896. Complete recovery was made without treatment. Although the presence of an anemia is usually convincing evidence against the diagnosis of infectious mononucleosis and in favor of some other condition as leukemia it should be kept in mind as evidenced by the cases cited above that a severe anemia may occur occasionally in this disease.

Results of Bone Marrow Aspiration.—Using sternal marrow a number of investigators including Morrison and Samwick (83), Israels (84) and Halcrow, Owen and Rodger (85) have noted an increase in the lymphocytes in the marrow. On the other hand Vogel and Bassen (86), Mendell, Meranze and Meranze (87) and Limarzi and his associates (88) have observed no evidence of a lymphoid infiltration but noted myeloid hyperplasia with inhibition of granulocytic maturation. The latter authors reviewed the literature on this subject to 1946. They report from their own observations that despite the large number of atypical lymphocytes in the peripheral blood in infectious mononucleosis the bone marrow is not involved except for evidences of myeloid hyperplasia and immaturity. Bone marrow aspiration in their opinion with which I concur is of diagnostic aid in differentiating infectious mononucleosis and other benign non leukemic conditions from lymphatic leukemia.

Sternal aspiration as a method of depicting the actual state of the marrow in this disease has been criticized properly by Campbell (89) who states that when fluid is aspirated from the marrow it is contaminated with blood from the vessels and that this introduces into the smears many of the cells characteristic of infectious mononucleosis. He states therefore that the extent of marrow involvement can only be determined by histological examination. Here also there has been discordant results reported. In the recent study by Custer and Smith (41) they state that the bone marrow contains no abnormal cells apart from those in the circulating blood. The marrows in their cases were either normal or moderately hyperplastic the latter when present being limited to the granulocytic series although megakarocytes occasionally seemed to be more numerous than usual. In a study by Campbell (89) in which material obtained by sternal puncture was examined histologically he reports that in 12 of the 15 patients there were foci of atypical lymphoid hyperplasia such as have not been seen in the marrow of any other condition.

A study of the bone marrow aspirated on the tenth day of the illness of two patients with infectious mononucleosis was made by Schleicher (90). Imprint and histologic preparations of marrow particles showed reticulum hyperplasia development of abnormal (leukocytoid atypical) lymphocytes *in situ* and reticulo epithelioid granulomas. This investigator was unable to verify the belief of other observers that the bone marrow reticulum is not involved in infectious mononucleosis.

Serological Reactions—The presence of sheep cell agglutinins in abnormally high titer or the Paul Bunnell (*15*) test as it has been called is known to be positive at some time during the course of the disease in a high percentage of cases of infectious mononucleosis and is rarely so in other conditions It is therefore a valuable diagnostic aid and should be employed in every instance when the diagnosis of infectious mononucleosis is suspected

The test based upon the principle recognized by Forssman in 1911 (*17*) was discovered to be positive in the disease by Paul and Bunnell in 1932 (*15*) The principle of the test, as applied to this disease is as follows Normally it is known that human blood serum contains agglutinins which in a titer of 1 4 or 1 8 but rarely higher will react positively with sheep red blood cells causing agglutination In the first week of the disease the reaction may be positive in a dilution as low as 1 16 but in the second and third weeks the titer may reach 1 256 or higher Positive reactions in dilutions as high as 1 2000 or greater have been recorded It is known that sheep cell agglutinins may appear several days prior to the characteristic changes in the circulating lymphocytes and furthermore that a positive reaction may precede the enlarged lymph glands or other clinical evidence of the disease

In Contratto s (*21*) group of 196 patients the heterophile antibody test was done in 143 or 73 per cent of the series Of these agglutination occurred in a dilution of 1 64 or higher in 118 cases or 82 4 per cent and the serums did not agglutinate the cells in 25 In the experience of this observer with which I concur it is a common occurrence that a heterophile test made early during the infection might not show the agglutination in a high titer while the serum from the same patient taken several days or a week later would show the presence of agglutinins in a dilution of 1 64 or higher In a few follow up heterophile tests which he did it was found that the results were negative within three months after the patient s discharge from the hospital

In a comprehensive study of the heterophile antibody reaction Kaufman (*91*) found that the test was positive in 75 per cent of his patients with infectious mononucleosis Other conclusions of this observer in regard to the test were that the reaction may become positive as early as the third day but sometimes not until the second month or not at all the reaction usually remains positive for two to four months although it may persist for nine to 12 months a positive test supports the diagnosis of infectious mononucleosis but a negative one does not rule it out certainly the test has great clinical value especially if repeated at intervals in fevers of unknown origin

Our experience with the heterophile antibody agglutination reaction indicates that it is a valuable laboratory aid in the diagnosis of infectious mononucleosis In a series of 158 patients at the University of Michigan

with clinical evidence of the disease the reaction was positive in all patients when several tests were done and special precautions were taken to eliminate errors of technic according to Zarafonetis (22) This observer emphasizes two exceedingly important points in regard to the test First certain technical errors may give rise to incorrect results For example the accuracy of the test varies with the concentration of sheep cells the cells should not be over one week old (92) the titer varies with the cells of different sheep and a "false reaction" may result from cold agglutinins which can be averted by immersing the preparation in the water bath for two hours Perusal of the articles by Keiper (92) and by Zarafonetis (22) are helpful in giving a clear understanding of the difficulties of technic pertaining to the reaction Second of great importance is the insistence that at least two and preferably more tests be done and that *more confidence be placed on whether the titer is rising or falling than on the level of the titer of any given specimen* Titers that remain constantly at the same level for a long period of time as they occasionally do are not likely to be indicative of the diagnosis of infectious mononucleosis For example one patient with polycythemia and gout studied by Zarafonetis (22) had a positive agglutination titer of 1 512 which remained constant in many tests over a year No explanation of this was apparent but it certainly was due to some other cause than infectious mononucleosis

In general it can be said that the test may remain positive for a period of two to five months but it may revert to normal in six to eight weeks The frequency of a positive test in this disease is great therefore if the blood is tested after the first week of the disease and even in the initial period there is a high percentage of positive results *Hence in all patients the test is likely to be positive in a dilution of 1 128 or greater provided it is repeated a number of times On the other hand it should be emphasized that in the presence of other convincing evidence of the disease a negative Paul Bunnell test should not by any means eliminate the diagnosis of infectious mononucleosis*

Although sheep cell agglutinins have been searched for in many other diseases they have been found to be present and then only occasionally in a few other conditions The reaction was studied in 2000 cases representing 76 different clinical conditions by Paul and Bunnell (15) and in none was there a positive reaction at a titer which is found in infectious mononucleosis According to Bernstein (9) an increased titer has been reported as occurring occasionally in scarlet fever rubella tuberculosis and filariasis This observer also states that the injection of liver extract may produce agglutination in titers as high as 1 1280 but this has not been confirmed nor has it been true in my experience The fact that the test is generally regarded as uniformly negative in leukemia is of the greatest assistance in differentiating it from infectious mono-

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Although sheep cell agglutinins have been searched for in many other diseases they have been found to be present and then only occasionally in a few other conditions The reaction was studied in 2000 cases representing 76 different clinical conditions by Paul and Bunnell (*15*) and in none was there a positive reaction at a titer which is found in infectious mononucleosis According to Bernstein (9) an increased titer has been reported as occurring occasionally in scarlet fever rubella tuberculosis and filariasis This observer also states that the injection of liver extract may produce agglutination in titers as high as 1 1280 but this has not been confirmed nor has it been true in my experience The fact that the test is generally regarded as uniformly negative in leukemia is of the greatest assistance in differentiating it from infectious mono

nucleosis Recently however Carpenter Kahler, and Reilly (93) have reported elevation of the heterophile antibody titers varying from 1–128 to 1–896 in two patients with leukemia one having the myelomonocytic and the other the Shilling type of the disease In both cases the reaction had the normal type of absorption characteristics

The absorption test was devised by Davidsohn (94) to differentiate sheep cell agglutination due to the injection of horse serum from that caused by infectious mononucleosis According to Zarafonetis (22) some workers have apparently noted discrepancies in the results obtained from this test Furthermore as pointed out by Zarafonetis modern therapy has practically eliminated the use of horse serum in this country and hence the problem of a false reaction due to this cause will not be encountered often

The heterophile antibody agglutination test may become positive in viral hepatitis but the incidence of such positive tests is in dispute For example it was observed by Eaton and his associates (95) that 34 per cent of a large group of patients in the acute phase of hepatitis developed a heterophile antibody which agglutinated the patients red blood cells in a titer of 1 40 or greater The titer however, rarely rose above 1 60 and the reaction could be differentiated from that appearing in patients with infectious mononucleosis by absorption with boiled guinea pig kidney and human liver The findings of Havens Gambescia and Knowlton (96) are not in accord with those of the previous observers cited The former found that only 16 of 508 patients (3 per cent) developed positive heterophile antibody tests with titers of 1 56 which were reduced to 1 7 or a negative reaction by absorption with boiled guinea pig kidney A rise or fall however could be demonstrated in weekly serial determinations It must be admitted therefore that a positive heterophile agglutination reaction may be observed in a small per cent of patients with viral hepatitis and that the titer will rise or fall when several determinations are made during the course of the disease The small per cent of positive reactions (3 per cent) the low positive titer and the fact that absorption with boiled guinea pig kidney reduces the titer to lower levels should be of assistance in differentiating between the reactions observed in the two diseases

False Positive Reactions for Syphilis in Infectious Mononucleosis —It is now generally recognized that false positive serologic reactions for syphilis appear in 18 to 20 per cent of all patients with infectious mononucleosis If additional samples of blood are tested in those cases in which negative test is first obtained it is likely that the incidence of a positive reaction would be even higher The Kahn reaction was positive in 10 per cent of all patients of a small group of patients with infectious mononucleosis tested at the University of Michigan Hospital This false type of reaction occurs with both the Wassermann and flocculation varie

ties of serological tests It is of the greatest assistance in evaluating such tests to know that the *positive phase in infectious mononucleosis persists for only a few days or weeks* but occasionally it may be present as long as several months According to Kahn (97) the tests will usually become negative within a few days or weeks

A consideration of the entire question of false positive serological tests for syphilis with a discussion of the incidence and possible causes of the positive tests in infectious mononucleosis and a review of the literature is given by Davis (98) He states that fortunately the reactions in infectious mononucleosis are usually very transient and weak whereas those of secondary syphilis are found to be of high titer if quantitated This author also discusses the relation of the heterophile antibody to sheep cells which might be of importance as antisheep cell hemolysin (amboceptor) is a reagent in the Wassermann test In his opinion however there is conclusive evidence against this factor which is furnished by the following considerations 1 flocculation tests are also frequently positive although antisheep cell hemolysin plays no role in these 2 there is no correlation between the heterophile antibody titer and serological tests and 3 absorption of a few such sera with sheep cells has removed the heterophile antibody without appreciably affecting the serologic tests

False positive reactions in this disease should be kept in mind because they may lead to the incorrect diagnosis of syphilis This is of special importance in relation to the required certificate stating that the applicants have a negative serological test for syphilis before a marriage certificate can be issued in some states Furthermore it is of course possible that a patient may have syphilis and also acquire infectious mononucleosis An example of such an association was called to my attention by Zarafonetis (22) The details of the serological tests are shown in table taken from the article written by him It will be noticed that the sheep cell agglutination titers over a period of 329 days became progressively less whereas the serological reaction for syphilis became increasingly stronger as measured in Kahn units

It is of interest to note that increased titers for cold agglutinins have been found to occur in the blood of patients with infectious mononucleosis by Spingarn and Jones (99) They observed a titer which varied from 1 56 to 1 3584 in seven patients with this disorder

Differential Diagnosis —The disease is so protean in its manifestations that it must be differentiated from a large number of conditions including Hodgkin s disease leukemia acute lymphocytosis acute tonsillitis Vincent s infection secondary syphilis agranulocytosis acute infectious hepatitis encephalitis meningitis poliomyelitis the Guillian Barre syndrome and various skin conditions as German measles and scarlet fever In some patients especially in the early stages of the disease the syndrome of fever without obvious cause may be presented In others the

clinical picture may be one of acute abdominal pain suggesting the need of surgical interference. So many conditions may be simulated that the *only safe course to follow from a diagnostic standpoint is to consider the* disease in the differential diagnosis of every febrile condition observed in infants, children *and young adults in which the nature is obscure.*

The lymphadenopathy may suggest Hodgkin's disease, lymphatic leukemia, or enlarged glands from sepsis. It should be emphasized that the nodes of infectious mononucleosis are slightly tender but they never develop a draining sinus except in exceedingly rare conditions in which there is a secondary infection. The fact that they are tender should differentiate them ordinarily from the enlarged glands of Hodgkin's disease and leukemia, and as there is usually a generalized enlargement, a local sepsis is not suggested.

When the patients are first seen, the presenting symptom is often one of fever without obvious cause. In one of my cases the temperature was elevated to the vicinity of 103 to 104 degrees (F.), there was a leukopenia of 6000 cells per cubic millimeter, and the differential formula was approximately normal. *The spleen was palpable but there was no enlargement* of the lymph glands at that time. The diagnosis of typhoid fever *was entertained tentatively. After the first week the sheep* cell agglutinins developed in the circulating blood and other typical features of the disease left no doubt as to the diagnosis of infectious mononucleosis. Other febrile conditions which may be suggested during the first week, especially, are influenza and various acute infectious diseases. This is doubly true of the latter when a skin rash is present. A case is reported by Leavell and McNeel *(100)* which closely simulated Rocky Mountain spotted fever. This patient had the history of a tick bite, unexplained fever, palpable spleen, with positive agglutination reactions for both sheep cells and Proteus X 19. It is certainly true that in the case of any obscure fever in a child or young adult, the blood should be tested routinely for the presence of sheep cell agglutinins.

It is pointed out by Rubenstein and Shaw *(101)* that in some instances infectious mononucleosis may simulate brucellosis as in both diseases fever of obscure origin is usually the outstanding feature of the clinical course and glandular enlargement may be present in the two conditions. In an effort to throw light on the frequency with which these two *diseases were confused from a* diagnostic standpoint they performed a heterophile antibody test on a series of 1000 consecutive blood specimens submitted by physicians to the State Bacteriological Laboratory of Massachusetts *for undulant fever agglutination* tests. In 100 tests it was found that a positive sheep cell agglutination in 1:128 or higher occurred in 13 specimens and a positive undulant fever agglutination was present in a titer of 1:405 or higher in 36 patients.

Agranulocytosis must be considered as a diagnostic possibility in some cases when the mouth and throat lesions are extensive and the leuko-

penia is pronounced Occasionally the total white blood cell count may be below 2000 per cubic millimeter and the neutrophils be less than 10 per cent These blood changes usually are limited to the first week of the disease and hence the diagnosis becomes clear with further observation

In some cases with extensive involvement of the mouth and throat the possibility of Vincent s angina diphtheria and "streptococcus sore throat" must be considered

A not uncommon and highly important decision to make is whether a patient is suffering from infectious mononucleosis or some type of leukemia Every year at the Simpson Memorial Institute it is necessary to differentiate between these two diseases in a number of cases which are referred for a decision Truly this is an important differential diagnosis for leukemia always terminates fatally whereas complete recovery is the rule in infectious mononucleosis The latter disease may simulate leukemia especially if there are enlarged glands a palpable spleen and atypical cells in the circulating blood Time of course always differentiates unfailingly between the two disorders but an immediate decision is desirable and this can usually be made by an experienced hematologist who can recognize unquestionably the abnormal cells of infectious mononucleosis and those characteristic of leukemia Other diagnostic points favoring infectious mononucleosis are the absence of anemia the presence of a normal number of blood platelets and the positive Paul Bunnell test

In some cases the presenting symptoms are referable to the nervous system and the entire clinical picture may simulate either meningitis encephalitis poliomyelitis or the Guillain Barre syndrome (infectious neuronitis) In others the chief complaint may be abdominal pain and when this is combined with nausea and vomiting fever and a leukocytosis which are not uncommon accompaniments the possibility of misleading a surgeon into performing an abdominal operation is sometimes great

The differential diagnosis between acute infectious hepatitis and infectious mononucleosis may be an exceedingly difficult one In both disorders there may be jaundice evidence of hepatic dysfunction abnormal lymphocytes in the circulating blood and lymph node enlargement It should be kept in mind however that in epidemic hepatitis upper respiratory symptoms are absent the abnormal lymphocytes are rarely observed and if seen are few in number lymphadenopathy is unusual and in only about 3 per cent of the patients according to Havens Gambescia and Knowlton (96) is there a positive heterophile antibody test

One serious mistake in diagnosis which is made in connection with this disease is to consider that the patient has syphilis This is because in from 18 to 20 percent of the patients all of the serological tests for syphilis are positive In addition the patient may have enlarged glands and possibly a maculopapular rash which may be mistaken for a syphilitic infection As a result of an attack of recent infectious mononucleosis

an acquaintance of mine experienced some difficulty in obtaining a marriage certificate as her premarital Kahn reaction was positive for a brief interval It is of importance to know that the positive serological reaction for syphilis in this disease is transient and a negative report usually results from the repetition of the tests every few days Occasionally the positive reaction may persist for several months

In summary it is apparent that infectious mononucleosis is exceedingly diverse in its symptomatology and may simulate closely a number of important diseases Such errors are responsible for an incorrect prognosis or improper treatment The following helpful suggestions concerning the diagnosis should be kept in mind 1, the incorrect diagnoses are usually eliminated by a sufficient period of observation

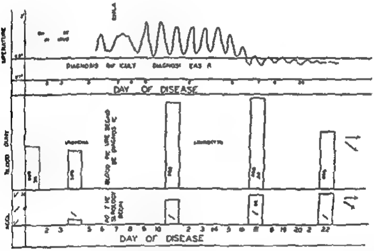

Fig. 70 —This diagram illustrates the difficulty which may be experienced in the diagnosis of infectious mononucleosis especially in the first week of the illness At this time the symptoms may be vague and mild there is a leukopenia often the percentage of lymphocytes is not increased and the heterophile antibody reaction is positive only in a low or doubtful dilution Later as depicted in the chart the fever the blood changes and the heterophile antibody reaction become diagnostic of the disease The fever is shown to persist for a period of 17 days which is the average duration There are wide variations in this phase of the disease however as indicated by patients who have a slight fever for a few days and those in whom the febrile course is severe and prolonged sometimes with relapses (Paul courtesy Bulletin of the New York Academy of Medicine)

2, the condition is almost always limited to infants children and young adults 3 the presence of generalized enlargement and tenderness of the lymph nodes a diagnostic titer of sheep cell agglutinins in the circulating blood and the presence of 50 per cent or more of the characteristic cells of infectious mononucleosis may be delayed for the first week of the disease but eventually at least two and usually all three of these criteria of the disease will appear and 4 the disease tends to occur in

epidemics hence examination of other children in the household or neighborhood will sometimes reveal other mild cases which lend support to the diagnosis of infectious mononucleosis

Infectious Lymphocytosis—According to Smith (*102*) two types of conditions are encountered in young patients which are characterized by lymphocytosis and are consequently confused with infectious mononucleosis or even with leukemia In one type there is a transient unexpected hyperleukocytosis with an absolute and relative increase in lymphocytes which is unassociated with recognizable symptoms or physical signs The second type which is more common follows infections of the upper respiratory tract of varying intensity It is characterized by fever of low grade present for weeks or months and associated symptoms which frequently include anorexia pallor fatigability para umbilical pain and diarrhea The latter is said to be a common complaint In both conditions there is a preponderance of lymphocytes in the blood with a normal or moderate elevation of the cell count Usually the disease occurs in children under 10 years of age but a few cases have been seen in the armed services in persons ranging from 19 to 29 years of age (*103*)

These two syndromes are classified as acute and chronic infectious lymphocytosis and are differentiated clinically hematologically, and serologically from infectious mononucleosis leukemia and miscellaneous infections commonly associated with lymphocytosis The lymph glands and spleen are usually not enlarged the sheep cell agglutination test in patients with either condition is negative and the bone marrow shows only an increase in lymphocytes The literature dealing with this disorder is reviewed by Moyer and Fisher (*103*)

Two cases of the first type reported by Smith which the author designates as acute infectious lymphocytosis were encountered in children two and one half and six years old The leukocyte counts were 92 000 and 44 300 per cubic millimeter and the lymphocyte percentages 86 and 79 respectively The course of the disease in each child was benign and in neither was there lymphoadenopathy enlargement of the spleen or the clinical evidence characteristic of infectious mononucleosis or of leukemia The results of the sternal puncture eliminated leukemia from consideration and the blood picture could be readily differentiated from either infectious mononucleosis or leukemia In neither instance was the sheep cell agglutination test positive An eosinophilia exceeding 500 eosinophils per cubic millimeter is commonly present as first pointed out by Finucane and Philips (*104*) and emphasized by Moyer and Fisher (*103*)

This may be the condition reported as atypical infectious mononucleosis by Reyersbach and Lenert (*42*) who observed 16 cases in 108 patients receiving convalescent care for rheumatic fever None of the

children had symptoms or physical signs of any kind The condition was discovered accidentally because of routine blood examinations The maximum leukocyte counts of the 16 children varied from 18 400 to 59 300 cells per cubic millimeter and the proportion of lymphocytes rose to a maximum of 93 per cent and was never lower than 71 per cent in any of the patients at the height of the disease The predominating cell was of the normal small lymphocyte type The large atypical lymphocytes characteristic of infectious mononucleosis were not present The sheep cell agglutination test was negative in each instance

The second type of case designated by Smith as chronic infectious lymphocytosis according to him occurs most commonly in infants and young children and is encountered frequently in pediatrics practice This group includes cases in which after an infection of the upper respiratory tract, a low grade fever continues to be present for prolonged intervals Associated symptoms are those which are usually observed in any chronic infection The blood in such cases shows a moderate leukocytosis with an increased lymphocytic percentage instead of the anticipated neutrophilic response The total leukocyte count varies in these cases from slightly above normal to 16 000 or 20 000 per cubic millimeter and the lymphocytes are commonly found to comprise 70 to 80 per cent of the white blood cells In neither type of the disease is there a significant change in the red blood cells or hemoglobin of the circulating blood It is considered by Smith that acute and chronic infectious lymphocytosis are separate clinical entities, although there is some evidence that they may be related It is his belief that the etiologic agent of each type is probably an undetermined virus which is related to an infection of the upper respiratory tract

The disorder is to be differentiated from infectious mononucleosis the lymphoid reaction in whooping cough and chicken pox and from acute and chronic leukemia The outlook is excellent as all cases observed have recovered the acute symptoms are usually present for a week to 10 days but the changes in the blood may persist for 10 days to six weeks and in some instances somewhat longer There is no treatment of proven value As the disease may have a virus etiology aureomycin may be given a trial Otherwise the treatment is purely symptomatic

Prognosis and Treatment —The average case of infectious mononucleosis runs its febrile course in 10 days to two weeks Following this acute phase there is often a convalescent period which persists for an additional two or three weeks at which time the only remaining symptom is ease of fatigue In some patients however after the body temperature declines to approximately normal there may be slight daily rises continuing for several weeks

The length of hospitalization as determined in a group of patients with infectious mononucleosis studied by Contratto (21) is a fair meas

ure of the duration of the patient's acute illness It does not of course indicate the entire period of the disease because the convalescence may be greatly prolonged and the patient may have been ill for some time before admission Forty five per cent the greatest number of his patients were hospitalized for six to 10 days 15 per cent for less than five days 42 per cent were confined for a period from 10 to 15 days 11 per cent for 15 to 20 days and 6 per cent from 20 to 25 days Two of his patients were obliged to remain for 31 days

Experience especially in more recent years has indicated that this disease can no longer be considered a benign one in all instances Occasionally the patient may appear critically ill and sometimes succumb from such complications as involvement of the nervous system thrombocytopenic purpura with anemia hemorrhage jaundice and rupture of the spleen either spontaneously or from slight trauma Nine necropsies are reported by Custer and Smith (*41*) which were observed while the authors were on duty at the Army Institute of Pathology Washington D C The cause of death in the nine cases was spontaneous rupture of the spleen in four Guillain Barré syndrome in two nasopharyngeal hemorrhage in one laryngeal edema in one and airplane accident in one convalescent patient The immediate causes of death in the four patients with ruptured spleens are listed as hemorrhage in two postoperative pulmonary embolism in one and blood transfusion reaction in one In addition in three other cases the ruptured spleen was removed and the patients recovered In at least three additional cases rupture of the spleen has been reported by other observers (*39 67 105*) Gooding (*106*) stated that death occurred in one of his patients with the disease from a bronchopneumonia Empyema has been noted as one of the rare but serious complications (*107*) When the great incidence of the disease is considered however it should be emphasized that the disease seldom causes the patient to suffer a severe illness and in only exceedingly rare instances does it prove fatal

In some patients recovery may seem to be complete and then after an interval of several weeks to several months there may be a relapse It is known that the abnormal lymphocytes may persist in the peripheral blood for months and occasionally they are said to be present even for years The enlarged glands become non tender shortly after the acute phase of the disease subsides but they may not return to an entirely normal condition for some months The Paul Bunnell test may remain positive for several months

It is the experience of Contratto (*21*) when a patient is asymptomatic but still has a significant increase in the white blood cell count and a definitely lowered polymorphonuclear count he is more likely than not to relapse if permitted to return to his normal activities He is inclined to consider this as a continuation of his illness rather than a relapse or

recurrence In his experience there was no instance of a continuation recurrence or relapse when he was absolutely certain that the patient had fully recovered as manifested subjectively and objectively with at least a beginning of a return to normal of the white blood cell count and the blood smear before being permitted to resume normal activities

In general it may be said that the average patient with the disease experiences the acute symptoms for about 2 weeks and that this is followed almost invariably with a period of convalescence characterized by asthenia which has a duration of several weeks but this may be unduly prolonged There are all types of variations from the average course of the disease In some the complaints may be so mild that bed rest or consultation with a physician is not thought necessary by the patient In other patients however the acute phase may persist for a month or more and the convalescent interval for six to eight months

All observers are in agreement that there is no specific *treatment* for the condition but experience has shown that many of the more severe manifestations might be avoided if the patient is put to bed early in the course of the disease Any therapy which is given is generally considered to be on a symptomatic basis Hence it is usually advisable to prescribe simple remedies as acetylsalicylic acid or codein if necessary for headache and generalized aches and pains As Vincent's organisms are frequently secondary invaders in the mouth and throat it is often helpful to employ hydrogen peroxide one half strength as a gargle and mouth wash In some instances roentgen ray therapy has been applied to the throat but to me this does not seem wise as a routine procedure and further experience is needed before a final opinion can be expressed concerning the value or possible dangers of this therapeutic agent

With the introduction of the sulfonamide drugs it is to be expected that they would be utilized as therapeutic agents in this disease At *present* the general *opinion* is that they are of no value in the control of the primary cause of infectious mononucleosis but they may be of importance in combating the complicating symptoms arising from organisms which are secondary invaders Antibiotic preparations however such as penicillin and especially aureomycin are superior for this purpose

After an extensive study of 99 patients with infectious mononucleosis who were treated with intramuscular injections of *penicillin* given twice daily and 67 control patients it is concluded by Bennike (*108*) that penicillin treatment is scarcely indicated in the disease as a routine form of treatment but that it probably has an effect in preventing complications in patients with secondary streptococcic infection *The results from* treating this disorder with *aureomycin* in nine patients is reported by Carter and Sydenstricker (*109*) and the literature on this subject is reviewed They state that in each instance a beneficial effect was observed and in one patient with severe angina there was a dramatic

response to the drug when given intravenously. It is their opinion that these observations when considered with those previously reported warrant further clinical trial of the preparation. The dose should be 250 to 500 milligrams orally every six hours or in patients who are seriously ill from 100 to 200 milligrams may be given intravenously every four hours.

Convalescent serum obtained from patients who have recovered from the disease and been afebrile for one to two weeks has been found valuable in total doses of 50 to 300 cc (*52*). I have had no experience with this form of therapy and would not employ it unless the patient were seriously ill and only after aureomycin had been given a trial. Gamma globulin in the treatment of the anginose type of the disease has been used by Bower, Affeldt and West (*110*). They conclude that the results are superior to those attained with penicillin and recommend a further trial. I have had no experience with this form of treatment and do not believe it can be accepted without additional critical evaluation.

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CHAPTER XIX

AGRANULOCYTOSIS

Synonyms—Agranulocytic angina granulocytopenia idiopathic malignant or pernicious leukopenia

Definition—Agranulocytosis is an acute or subacute disorder almost if not always due to an abnormal sensitivity to some drug characterized by a striking diminution or complete absence of the granulocytes from the circulating blood usually associated with a decrease in the total white blood cell count by a secondary infection involving chiefly the mucous membranes especially of the oral cavity and throat and producing constitutional symptoms There are no associated changes in the red blood cells or platelets, no hepatomegaly or splenomegaly and only local lymphadenopathy associated with sepsis If the causative drug is eliminated and appropriate antibiotic therapy instituted early in the course of the disease recovery usually results

In addition to true agranulocytosis included in this chapter are three other conditions characterized among other findings by a pronounced granulocytopenia Descriptions of these disorders are to be found at the end of this chapter They have in common however chiefly the diminution in granulocytes of the circulating blood and in some instances lesions of the mucous membranes In general it must be said that they are distinctly different diseases than agranulocytosis

History—The history of agranulocytosis is interesting to consider because its recognition as a clinical entity is of relatively brief duration This must necessarily be so because the essential diagnostic features of the syndrome are the changes in the blood Without reliable blood examinations as evidence in any given case it is nothing more than fruitless speculation to judge from the record whether a patient did or did not have the disease

From a consideration of all data it seems clear to state that the following are reasonably well established facts (1) the disease may have occurred occasionally before 1902 when Brown s case (*1*) was first reported but this is impossible to prove (2) although the condition did exist before 1922 it occurred rarely there are several authentic cases in the literature and undoubtedly others were observed but were not reported and (3) the increased frequency of the disease dates from the time of Schultz s classical description of it in 1922

In studying the historical development of our knowledge concerning this condition it should be remembered that accurate apparatus for counting the white blood cells was not in general use until the modern counting chamber was devised by Gowers in 1877 (see ref page 692 on Leukocytes) Although alterations in the number of leukocytes were recognized in 1845 when leukemia was first described variations in their numbers in disease states was not universally known until many years later The changes in the proportions of the various types of leukocytes was first generally employed following Ehrlich's (2) work in 1892

It should also be kept in mind that this condition is almost always due to some drug the earliest and most common causative one from 1922 for a period of 10 or 15 years being aminopyrine This preparation was marketed under the trade name of "pyramidon" A personal communication from Paul N Leech Secretary of the Council of Pharmacy and Chemistry and Director of the Chemical Laboratory of the American Medical Association written in 1934 has this to say in regard to the drug "Amidopyrine was prepared by Stoltz in 1893 and was patented in Germany in 1897 under the proprietary name Pyramidon Pyramidon has been on the American market for at least 25 years (note at least since 1909) under the pharmacopoeial designation amidopyrine the drug has been marketed by American Manufacturers for approximately 12 years" (namely since 1922) Not only was the drug sold as pyramidon" but it also was combined with numerous barbiturates and sold under a name which did not give any indication that aminopyrine was a component of the preparation The earliest examples of such a product were Allonal and Peralga which were first sold to the public as early as 1924 their introduction was soon followed by similar combinations which were prepared by many other drug firms of Europe and this country

This information is cited because it is undoubtedly of importance in evaluating the causes for the increase in incidence of the disease after 1922 Since it is now recognized that agranulocytosis is usually due to the action of various drugs such as aminopyrine arsenic in the form of arsphenamine gold dinitrophenol the sulfonamides and more recently thiouracil it is to be expected that the disease would be a "new syndrome for these preparations have only been used extensively in medicine in comparatively recent years

A Consideration of the Early Cases —It was not possible to state positively that cases of the disease occurred unless blood studies are available The contention by Pepper (3) that patients with "Putrid Sore Throat" may have had agranulocytosis lacks convincing proof although no one can deny that in a large group of such cases there may have been an occasional one of agranulocytosis

Among the earlier cases with complete blood studies there appear at least to be two in which the diagnosis of agranulocytosis is acceptable

They are the case described by Philip King Brown of San Francisco in 1902 and the one recognized by Turk in 1907.

The case described by Brown (1) was a 29 year old female who had been operated upon for a lacerated cervix and peritoneum. About three weeks after the operation, signs of a severe infection developed with chills, fever as high as 105.4 F, and complaints of sore throat. There was swelling and redness of the throat and finally membrane formation which yielded on culture only *Staphylococcus pyogenes albus and aureus*. The blood examination showed a hemoglobin of 65 per cent, red blood cells 3,240,000 per cubic millimeter, white blood cells 1000 per cubic millimeter, polymorphonuclears 1 per cent, small lymphocytes 82.5 per cent, large lymphocytes 16.5 per cent, and no eosinophils. Death occurred on the seventh day of the acute illness. On the day before death the white blood cell count was 260 per cubic millimeter with the following differential count: polymorphoneutrophils 21 per cent, myelocytes 2 per cent, eosinophils 2 per cent, large lymphocytes 18 per cent, and 59 per cent small lymphocytes. The decrease in the red blood cells was slight.

Here then was the case of a young woman who succumbed to an acute illness of one week's duration. The condition from which she suffered was characterized by chills and fever, extensive infection of the throat, a remarkable reduction of the total white blood cell count and an almost complete disappearance of the polymorphonuclear cells from the peripheral blood. A very slight anemia was present. There were no signs of a hemorrhagic disorder. Only two findings, however, cast slight doubt on the diagnosis of agranulocytosis and these are described in the following statement: The spleen, the cervical, supraclavicular, axillary, epitrochlear and inguinal glands were all slightly enlarged but not painful. At necropsy the spleen was said to be enlarged to the size of the open hand. In regard to this case Dameshek (4) has to say: In this case, which is unusually well described for the period, agranulocytosis seems probable, although in the view of the generalized lymphadenopathy and splenomegaly the possibility of aleukemic lymphatic leukemia cannot be ruled out. Plum says with reference to this case that it "would hardly be possible to decide with certainty whether this case died of Schultz's agranulocytosis.

In my opinion, if it had been possible to demonstrate that the patient had been given pyramidon, the diagnosis would be certain, but even as presented it appears to be an authentic example of the disease. It should be recalled that this drug was prepared in Germany in 1893 and patented in that country in 1897, hence it might have been available, although I have no exact knowledge of the exact time that it was introduced into the United States.

The information relating to this case was reviewed by Dr. Carl V. Weller, Professor of Pathology, University of Michigan Medical School

at my request In a letter to me dated December 11 1944 he made the following comments I think that there is no doubt that this is a true example of agranulocytic angina Those who question it must be questioning the *reason* for the agranulocytosis in this instance Those who have considered this to be an example of subleukemic leukemia must have assumed a leukemic replacement of the bone marrow and other hematopoietic tissue Since there is not a proportionate decrease in red blood cells and hemoglobin the bone marrow apparently was not replaced

As to the autopsy findings no evidence of leukemia or aleukemic lymphoblastoma appears in the gross or microscopic examination except for the apparently mild enlargement of the lymph nodes and spleen I believe that Doctor Ophuls would have mentioned it had there been any disturbance in follicular architecture He describes the liver as microscopically normal yet the liver is usually a very sensitive indicator of leukemic infiltration and of all forms of leukemic lymphoblastoma"

"It seems to me that this must be considered a genuine example of agranulocytic angina of undetermined cause

I discussed this matter with Doctor Brown shortly before his death and although he stated that he used pyramidon soon after it came to the attention of the profession in the United States it was not possible for him to say whether the patient in question had received it or whether he was using it in his practice at that time

The second case in the earlier literature is the one reported by Turk (5) in 1907 and this patient seems certainly to have agranulocytosis The patient was a woman 45 years of age who succumbed after an illness of 20 days from a condition characterized by chills and fever and necrotic lesions in the mouth and throat The red blood cell count was 5 255 000 per cubic millimeter hemoglobin 92 per cent the white blood cell count 940 per cubic millimeter with no polymorphonuclear cells Necropsy showed no evidence of leukemia or typhoid fever

The third case in the literature which Plum (6) considers to be suggestive of agranulocytosis was reported by Schwarz (7) in 1904 The patient was a boy age nine who succumbed to a brief febrile disease with gingivitis and swelling of the subaxillary glands The white blood cell count was 600 per cubic millimeter and the red blood cell count was 2 0 millions per cubic millimeter It appears likely that this patient did not have agranulocytosis but died of aplastic anemia or some form of subleukemic leukemia

Hence it must be concluded that prior to 1922 when Schultz made his original contribution there were reported only two cases which can be accepted as examples of this condition although of course others probably existed It can be said with certainty that at least the syndrome was exceedingly rare I can vouch for this from my own experience

Since graduation from medical school in 1917, I have been associated with hospitals in which a routine blood examination was made on all patients who were admitted. Furthermore, in all of these institutions there was a special interest in blood conditions. In no instance was a syndrome reported which resembled agranulocytosis until after Schultz had described the conditions in 1922. The blood changes are so striking that it is unlikely that they would be overlooked.

In an attempt to settle the question as to whether the condition occurred prior to 1922, Plum considered 54 739 case records including 24 175 cases of diphtheria from the Blegdam Hospital in Copenhagen. He found 15 cases in which the patient died with such clinical features that the diagnosis of agranulocytosis seems rather probable although it cannot be made with certainty because of the lack of blood examinations. He concludes from his investigation that agranulocytosis may have occurred in the Blegdam Hospital in 1916 and 1918 that the first probable case was found in 1922 and the first practically sure case occurred in 1923. After this there was one probable case in each of the years 1924 1926 and 1927. *The first altogether sure case of the disease* was seen in 1928 another case was diagnosed in 1929 and in 1930 the number of cases suddenly rose to 10. He states that most of the cases observed in Denmark were between the years 1930 and 1934. Lichtenstein (8) studied the records of the Epidemic Hospital in Stockholm for the decade 1916 to 1925 in which interval a total of 34 417 patients were admitted. In the years 1916 to 1920 there was no case which might have been agranulocytosis. In 1921 to 1925 there were probably seven cases and in the years 1926 to 1930 there were no less than 27 cases. The evidence seems to indicate that in general there were no certain cases of the disease admitted to these hospitals prior to 1922 that a few cases were observed between the years 1922 to 1929 and between 1929 and 1934 the disease reached its greatest prevalence.

The Contribution by Schultz and the More Recent History of the Disease.—It is generally accepted by all who are interested in the history of the development of our knowledge of agranulocytosis that the original contribution of Werner Schultz (9) marks the beginning of the world wide recognition and interest in the disease. His presentation was made before the meeting of the Verein fur innere Medizin und Kinderheilkunde at Berlin on July 3 1922. At this time he described five fatal cases in women in which there was a remarkable decrease in the total white blood cell count *especially in the granulocytes* associated with extensive ulcerative lesions of the mouth and throat. He attributed this condition to a reduction of the myelocytes and granulocytes in the bone marrow and suggested the name agranulocytosis. It is of interest that 17 years later in 1939 Schultz again published an article on the same subject in which he emphasizes that physicians should be on the

alert for the disease especially when they observed the combination of gingivitis and tonsillitis in association with severe sepsis In this paper he acknowledges that aminopyrine plays a leading etiologic role and that other drugs such as arsphenamine gold and more recently the sulfonamides may be responsible for the production of the syndrome He makes little comment on the various forms of treatment but warns that surgical intervention is contraindicated and that transfusion with leukemic blood is of little value In the year after the first report by Schultz the name agranulocytic angina was applied to the syndrome by Friedmann (*10*)

The first reported case in the United States was observed by Beatrice Lovett and appeared in November 1924 (*11*) Following the publication of the article by Schultz in 1922 reports of cases appeared throughout the world but especially in Germany England the United States and the Scandinavian countries By 1931 Dameshek (*12*) states that about 200 cases had been reported and in the interval between the years 1931 and 1934 the Department of Vital Statistics recorded 1981 deaths from the disease in the United States

Observations on the Bone Marrow—The earlier necropsy examinations revealed the presence of aplasia of the bone marrow in some cases Observation of the marrow in several fatal cases by Fitz Hugh and Krumbhaar (*13*) led them to formulate the theory of primary maturation arrest rather than primary aplasia to account for the facts

Development of Our Knowledge Concerning the Etiology of the Disease—In 1931 Kracke (*14*) read a paper before the meeting of the American Society of Clinical Pathologists held at Philadelphia June 7–10 in which he directed attention to his experimental work dealing with the production of agranulocytosis in rabbits by the subcutaneous injection of benzene in olive oil According to this investigator the course of the experimentally produced condition seemed to be similar to that observed in the human namely that at first there was a neutropenia then a generalized infection from organisms already present or from those introduced His views concerning the possible cause of the disease is expressed in the following paragraph contained in his paper written in 1931 The observations that the disease occurs largely in Germany and the United States that it occurs in middle aged white women for the most part in women of leisure or in women living under good economic conditions that it is seldom seen in the Negro that most of the patients had a history of previous medical care or treatment with various drugs that the coal tar series of drugs has its widest range in those parts of the world in which the disease is most frequent that these drugs and chemicals contain the altered or modified benzene ring and that benzene is the one outstanding leukocyte depressant *led me to believe that this substance or its*

products must be seriously considered as being the cause of the condition To Kracke must be given the credit of first pointing out clearly that some drug might possibly be the cause of the condition It is of interest to note that he tried to produce the disease in animals but without success by means of the following drugs given subcutaneously, intravenously or orally *amidopyrine* phenacetin peralga *dial* resorcinol pyrocatechin, orthocresol metacresol paracresol, phenol para oxybenzoic acid meta benzoic acid, and 50 per cent alcohol Among other things he concludes that The etiology of agranulocytosis is unknown but the benzene ring must be strongly considered

Conclusive evidence that aminopyrine could cause agranulocytosis in certain persons was first presented before the meeting of the Central Society of Clinical Research held in Chicago in October 1933 by

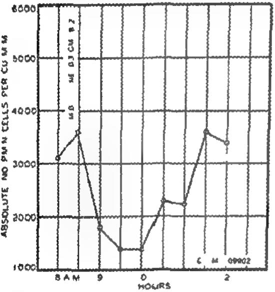

Fig 71 —Showing the effect of a single oral dose of 0 3 gram of aminopyrine on the neutrophils of the peripheral blood in a patient who had recovered from agranulocytosis (Sturgis and Isaacs courtesy *Transactions of Association of American Physicians*)

Madison and Squier Their communication first appeared in print in *the Proceedings of the Society published in the Journal of the American Medical Association* for December 23 1933 and a more comprehensive article dealing with the subject was printed in the same *Journal* for March 10 1934 (*15*) According to these observers their impression that aminopyrine might be associated with the cause of the disease dates to November 1931 when they observed two patients in whom the picture of agranulocytosis developed following the ingestion of allonal (allylisopropylbarbituric acid with aminopyrine) They were able to report observations on a total of 14 patients in whom the onset of granulocytopenia was directly preceded by the use of aminopyrine and concluded that this drug alone or in combination with a barbiturate is capable of producing the disease in certain individuals who have developed sensitivity to the drug They clinched their observations by administering aminopyrine in single doses of 0 3 and 0 7 gram to two

patients who had clinically recovered from the disease In both there was a temporary marked depression of the granulocytes following the administration of aminopyrine but in one amytal produced no such response These observations were later confirmed by Sturgis and Isaacs (*16*) and by Plum (*17*) and others

Hence it became established beyond the question of a doubt that aminopyrine was responsible for many cases of agranulocytosis and this at once became generally accepted It soon became known however that other drugs were also capable of producing the condition

Other Drugs as a Cause of Agranulocytosis—Following the introduction of salvarsan by Ehrlich in 1909 and neosalvarsan in 1912 various types of blood disorders following their use soon appeared in the literature Although it is known that they can cause a true agranulocytosis with a reduction in the white blood cells alone it should be kept in mind that more commonly there is likely to be a combination of leukopenia anemia or a hemorrhagic tendency Moore and Foley (*18*) in 1920 reported a case receiving salvarsan with a white blood cell count which fell to 600 per cubic millimeter with 0 5 per cent neutrophils but there was also a moderate anemia and purpura A patient who had all of the features of agranulocytosis except that a hemorrhagic tendency was present following neosalvarsan treatment was reported by Kastlin in 1927 (*19*) In 1928 comment concerning salvarsan as the cause of agranulocytosis was made by Aubertin and Levy (*20*)

Gold was first employed in 1924 as a therapeutic agent in tuberculosis The first case of agranulocytosis due to this therapeutic agent was reported by Jacob and Douady in 1930 (*21*)

The earliest reference to dinitrophenol as a causative agent in agranulocytosis is that of Hoffman Butt and Hickey in April 1934 (*22*) They report the case of a woman who developed the clinical picture in August 1933 after two weeks ingestion of the drug A second report of a similar case followed in July of the same year (*23*)

The relation of the sulfonamide drugs to agranulocytosis is one of great importance because it has been shown that each one of them which has come into general use may cause the condition Theoretically at least it is predictable that eventually cases due to the latter may be reported It will be recalled that sulfanilamide was introduced into medicine by Gerhardt Domagk in February 1935 at which time he showed that prontosil was effective in preventing death from experimentally produced streptococcus infection in mice It was at once recognized as a highly effective form of therapy in the treatment of certain infections and hence soon came into widespread use

The earliest recognition which I have been able to discover that agranulocytosis may occur as a complication following the use of the sulfonamide drugs is contained in a communication to the *New England Journal of Medicine* by Plumer (*24*) dated April 17 1937 In this

TABLE XLI

AGRANULOCYTOSIS DUE TO SULFADIAZINE
MALE AGE 70

			Gm	W B C
November 3 1941	Operation (Repair Strangulated Hernia)			9800
November 10 1941	SD	I V	5	7500
November 11 1941	SD	I V	5	
November 12 1941	SD	I V	5	
November 13 1941	SD	Orally	2	9000
November 14 1941	SD	Orally	6	
November 15 1941	SD	Orally	6	
November 16 1941	SD	Orally	6	
November 17 1941	SD	Orally	6	
November 18 1941	SD	Orally	4	12000
November 19 1941	SD	Orally	6	
November 20 1941	SD	Orally	2	
November 21 1941	SD	Orally	2	
November 22 1941	SD	Orally	2	
November 23 1941	SD	Orally	2	
November 24 1941	SD	Orally	4	
November 25 1941	SD	Orally	6	5350
November 26 1941			0	
November 27 1941	SD	Orally	4	
November 28 1941	SD *	Orally	3	1500
November 29 1941				850 *
November 30 1941	Death			

* Total Sulfadiazine Dosage 78 Gm in 20 Days
R B C 4 4 *HB* 73% M C V 86 C M PL 140,800 W B C 850 PMN 2% E 2% B 17 L 90% M 5% Sternal Marrow Maturation Arrest at Myelocyte Stage

TABLE XLI —A fatal case of agranulocytosis in a 70 year-old man who received 78 grams of sulfadiazine in 20 days as treatment of a postoperative pneumonia It is possible that this patient may have had a vitamin B deficiency as he was elderly and was said to be queer relative to his food habits In addition he had a stormy 28 day postoperative period with nausea and vomiting during which time his food intake was very much restricted

article he reports the case of a patient with subacute bacterial endocarditis who succumbed with the typical manifestations of agranulocytosis following the administration of "prontylin in 20 grain doses daily for a period of five weeks At the end of that interval there was an extensive gangrenous infection of the mouth and pharynx and a white blood cell count of 400 per cubic millimeter with no neutrophils No other drugs had been given to the patient A second case also suffering from subacute bacterial endocarditis is reported a short time later in the *British Medical Journal* for July 17 1937 by Young (25) in a 53 year old male who received 54 grams in 18 days of prontosil album

Sulfapyridine was introduced as a product superior to sulfanilamide in the spring of 1938 by Whitby (26) The earliest reference to agranulocytosis following the use of this preparation is by Johnston in 1938 (27) Following the introduction of sulfathiazole in 1939 by Fosbinder and Walter (28) Kennedy and Finland (29) were the first to

report agranulocytosis due to this drug The patient was also treated for subacute bacterial endocarditis and succumbed to agranulocytosis after receiving 1 5 grams every four hours over a period of approximately three weeks Sulfadiazine was synthesized in 1940 by Roblin and his associates (30) The first case of agranulocytosis caused by it was reported by Levin and Bethell (31) in April 1942 This was soon followed by the report of a similar case by Curry (32) which appeared in August 1942 The statement by Flink and Bratrud (33) published in October 1943 that there is "only a single case report of agranulocytosis being due to sulfadiazine" at that time is clearly due to an oversight

From the data reported above it was apparent that agranulocytosis might follow the use of sulfanilamide sulfapyradine sulfathiazole and sulfadiazine although the explanation for this was not known Another sulfonamide sulfaguanidine introduced in 1940 by Marshall and his associates primarily for its action on the flora of the gastro-intestinal tract has not been shown to date to be capable of producing agranulocytosis That this may eventually occur is to be surmised because in July of 1943 Johnson (34) reported the case of a patient which terminated fatally following the use of succinylsulfathiazole (sulfasuxidine) a preparation which has a similar action on the bacteria of the intestinal tract That such a condition could occur despite the fact that little if any of the preparation is absorbed is of importance from a practical and theoretical standpoint This clinical observation correlates with the experimental work of Spicer and his associates (35) who found that rats when given either sulfaguanidine or sulfasuxidine in purified diets develop agranulocytosis a leukopenia and hypocellularity of the bone marrow Furthermore they discovered that these alterations in the blood can be prevented or successfully treated with whole dried liver or with certain liver extracts This work led to the observation by Daft and Sebrell (36) that granulocytopenia and leukopenia in rats thus produced could be treated satisfactorily with crystalline folic acid

Etiology—Age and Sex Distribution —According to Plum (6) the condition occurs more commonly in females than males in a ratio of two or three to one Whitby and Britton (37) consider that it is three times more common in females The reason for this is not clear unless some unknown endocrine influence plays a role It is observed most frequently in adults between the ages of 40 and 60 years but it may occur at any age In a review of the literature Plum (6) found references to agranulocytosis occurring in only nine children A case in a newborn infant is reported by Slobody Abramson and Loizeaux (38) eight hours after delivery the white blood cell count was 4200 per cubic millimeter with only 1 per cent neutrophils and 1 per cent eosinophils in the circulating blood In this patient it was not thought that drugs

played a role in the causation of the disease but that it was probably due to sepsis. Treatment with whole blood transfusions and antibiotic agents was followed by recovery. The cases of two infants, aged 10 and 12 weeks, with agranulocytosis are reported by Givan and Shapiro (39) and Kato *et al.* (*40*) observed a fatal case in an eight week old infant following sulfathiazole therapy.

Drugs as the Cause of Agranulocytosis.—In my opinion, probably all cases of genuine acute agranulocytosis are secondary to some drug although this is sometimes difficult to prove. In almost all instances, however, it is possible to obtain convincing evidence of this from the history now that it is known what drugs are likely to cause the disorder. Occasionally, even after careful questioning, the patient will deny that drugs which may have a causative relationship have been taken and it is still remotely possible that rarely the condition may arise from some other cause which is not yet known. On the other hand, when con-

TABLE XLII

Name	*Age*	*Sex*	*W B C*	*PMN*	*R B C*	*HB*	*T T*	*Pent*	*Result*
R D	38	F	550	0	3.7	69	+	+	D
F M	28	F	2400	0	4.6	76	+	+	R
J D	41	F	1135	0	3.9	75	+	+	R
F F	26	F	1000	8	4.3	70	+	+	R
M H	45	F	300	4	—	—	+	O	D
F C	42	F	575	0	4.4	78	+	+	D
D K	41	M	800	0	3.7	84	+	O	D
S P	50	M	2200	6	4.5	85	+	+	R
V S	26	M	1350	4	4.8	83	+	+	R

TABLE XLII.—Data concerning the blood changes, treatment and outcome in nine patients with agranulocytosis observed at the University Hospital. These patients were observed at a time before the etiological significance of aminopyrine was appreciated. It was later possible in each instance, however, to prove that this drug had been taken by each patient just prior to the onset of the agranulocytosis. It has usually been given for migraine headaches or dysmenorrhea. It will be noted that four of the nine patients succumbed despite the administration of pentnucleotide. Doubtless some of these patients would have survived if the sulfonamides or penicillin had been available at that time, as sepsis was the cause of death in each instance. It should be noted that the polymorphonuclear percentages were below 10 per cent in all patients and in five of the patients these cells disappeared completely from the circulating blood. It is characteristic of the disease that these cells are greatly diminished, usually below 20 per cent, often below 10 per cent, and not infrequently they may be entirely absent. In this respect the blood picture differs from that of an overwhelming infection when there may be a pronounced leukopenia but the neutrophils are often in the vicinity of 50 per cent. It should be noted also that the red blood cell counts and hemoglobin percentages, while somewhat below normal, are not greatly reduced. This is a good differential point from the leukopenias associated with subleukemic leukemia in which the anemia is usually pronounced.

fronted with a patient who undoubtedly has the disease, and the patient will not admit having taken drugs which might have caused it, the most likely deduction is that the history is unreliable and inaccurate. A good example of this is shown in Figure 72. This shows the white blood cell

count of a patient who had two attacks of agranulocytosis but denied all possibilities of a drug etiology The cause was established later when copies of all the prescriptions written for her disclosed that she had been taking aminopyrine for rheumatism at intervals for many years

In summary then it is probable that all cases of acute agranulocytosis are due to a drug sensitivity but this cannot be established conclusively in every case In such instances it is likely that the history is unreliable but there still remains the possibility (1) that the patient may not have genuine agranulocytosis or (2) that in the so called idiopathic cases the cause has not been discovered

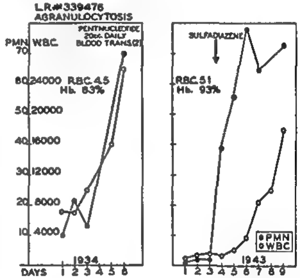

Fig 72—Blood changes in a middle aged woman who experienced two attacks of agranulocytosis 9 years apart On both admissions the diagnosis was obvious as indicated by the extreme reduction of the neutrophils in the circulating blood without important changes in the red blood cells or hemoglobin The one diagnostic element lacking was the etiologic agent The patient was discharged on both occasions with the diagnosis of agranulocytosis of the idiopathic type She was requested however to ask her physician for all prescriptions which had been given to her during the past 10 years When these were examined one which she had taken frequently during the 10 year interval for rheumatic aches and pains was found to contain aminopyrine On being given a test dose of this drug there was a definite reduction in the neutrophils of the circulating blood within a short interval, indicating that she was sensitive to it

It is often difficult to be certain if a given drug is the causative agent in any given case Before it can be stated that this is true it is necessary (1) to be positive that the patient has genuine agranulocytosis and is not suffering from acute sepsis or some other type of blood dyscrasia than agranulocytosis (2) that other leukocytic depressants are eliminated and (3) that the drug will produce a prompt striking and convincing decrease in the granulocytes of the circulating blood when given to a patient who has recovered

The following is a list of drugs which *are known positively to be* responsible for the *condition in patients who are apparently* sensitive to them

1 The sulfonamide drugs including sulfanilamide sulfapyridine sulfathiazole sulfamerazine sulfadiazine and succinyl sulfathiazole

2 Thiouracil propyl thiouracil and methyl thiouracil

3 Aminopyrine and closely related compounds as novaldin and causalin Due to the widespread knowledge that this drug may be responsible for agranulocytosis it is now not commonly used A case was reported in 1948 (*41*) however due to causalin each tablet of which contains 1 82 grains of aminopyrine I would not hesitate to employ aminopyrine which is an excellent form of therapy for rheumatic fever if the patient was unable to tolerate the salicylates provided the patient was under close observation in the hospital In fact I have done so in recent years The preparation is not however kept on the wards of the University Hospital in Ann Arbor for routine use but must be ordered from the pharmacy by special prescription which directs attention to the care which must be exercised in its use

4 Gold

5 Dinitrophenol

6 Organic arsenicals as arsphenamine neoarsphenamine and mepharsen

7 Presidon (pyrithyldione) a mild, non barbiturate sedative

8 Antihistaminic drugs as pyribenzamine diatrin and possibly other closely allied drug preparations

9 Tridione and mesantoin (antiepileptic drugs)

Other drugs or therapeutic agents which have been regarded by some as causing the condition but in my opinion they rarely if ever are responsible for the disease

1 The barbiturates
2 Antipyrine
3 Phenacetin
4 Neostibosan the diethylamine salt of stibanilic acid
5 Quinine
6 Cincophen
7 Bismuth
8 Nirvanol (phenyl ethyl hydantoin)
9 Plasmoquin
10 Streptomycin
11 Chloramphenicol (chloromycetin)
12 Phenylbutazone

The Sulfonamide Drugs —Shortly after the introduction of the sulfonamide drugs it became apparent that they too could cause this condition It has now become well established that almost all sulfonamides including sulfanilamide sulfapyridine sulfathiazole sulfadiazine and rarely succinyl sulfathiazole can act as the causative factor in this disease in some patients So far as I am aware no case yet has been reported as following the administration of sulfaguanidine

From my experience, there is evidence to suggest that the sulfonamides produce the syndrome of agranulocytosis under two different circumstances In one it follows a relatively large dosage over a considerable period of time during which interval the patient may become sensitized In the other the patient possibly becomes sensitized from previously taken doses and the condition develops after a comparatively small amount of the drug has been given

Succinyl Sulfathiazole and Agranulocytosis—It was generally considered when the sulfonamides succinyl sulfathiazole and sulfaguanidine were introduced into medicine for their action in inhibiting bacterial growth in the small intestine the possibility of producing unfavorable reactions was slight as they were absorbed only in negligible amounts That the amount absorbed was small even when large oral doses were administered over a long period of time was shown by the observation that often there was not a sufficient quantity of these substances in the blood stream to estimate quantitatively Nevertheless it is now known that agranulocytosis may follow the oral administration of succinyl sulfathiazole although there is no information indicating that sulfaguanidine has caused this condition in humans

The first case reported in the literature of agranulocytosis following the use of succinyl sulfathiazole is the one observed on the Dermatology service at the University Hospital Ann Arbor Michigan and reported by Johnson (*34*) The patient a youth of 19 years developed a fatal agranulocytosis after receiving a total dosage of 159 grams of the drug over a period of 17 days It is of interest to note however that on two previous occasions the patient had experienced reactions when taking sulfathiazole and receiving intravenous injections of typhoid vaccine In this patient the white blood cell count fell to 200 cells per cubic millimeter with a differential count showing small lymphocytes of 14 per cent and large lymphocytes of 86 per cent

In another patient whom I observed in the spring of 1943 there was a reduction in the polymorphonuclear neutrophil cells to 13 per cent with a white blood cell count of 12 750 per cubic millimeter after 12 grams daily for about six weeks had been given to the patient who had chronic ulcerative colitis There were no symptoms of agranulocytosis and the polymorphonuclear percentage gradually returned to normal after the drug was discontinued

It is of interest to speculate as to the cause of agranulocytosis following the use of such a drug which is not absorbed in appreciable quantities One possible explanation could be that such a patient gradually becomes sensitized to even minute amounts of the drug which may be present in the blood stream and the quantities are too small to estimate quantitatively Another more likely view is supported by the important experimental studies of Spicer *et al* (*35*) These investigators found that when either succinyl sulfathiazole or sulfaguanidine is given in

purified diets to rats the animals develop agranulocytosis and hypocellularity of the bone marrow. This condition can be prevented or treated successfully with whole dried liver or liver extract. The usual change in the blood is a reduction in the total number of leukocytes, and a decrease in the granulocytes often below 10 per cent. It has been suggested by the authors that these drugs produce the above effects by a lowering of the bacterial intestinal synthesis of certain essential growth factors or that there might be a direct toxic action, or possibly with an interference with the functioning of one or more enzyme systems of the body. At any rate there can be no question that at least one of these drugs (succinyl sulfathiazole) can when given uninterruptedly, or in large doses over a long period of time cause definite and sometimes fatal agranulocytosis in humans.

Elvehjem (*42*) has observed that monkeys fed on a synthetic diet deficient in vitamins showed a leukopenia similar to that reported by Day and his co workers. The leukopenia was observed to respond to the feeding of folic acid preparations. Furthermore Elvehjem confirmed the work of Spicer and his associates who had previously reported the consistent development of a leukopenia and agranulocytosis in rats receiving sulfaguanidine and succinyl sulfathiazole in synthetic rations. In addition he has shown that the leukopenia responds to the feeding of folic acid concentrates. It is interesting to note that in the monkey a leukopenia develops following a nutritional deficiency and in rats the same condition follows the administration of an intestinal antiseptic which destroys bacteria and hence their synthetic action in relation to the formation of vitamins is lost. In both conditions the leukopenia disappears following the administration of folic acid preparations.

An extension of the observations dealing with the production of agranulocytosis in rats by means of sulfasuxidine and sulfaguanidine has been made by Kornberg and his associates (*43*). They found that a severe granulocytopenia or anemia or both may be produced in rats given sulfathiazole sulfadiazine or sulfanilamide at a 1 per cent level in purified diets. It was also observed that the granulocytopenia thus induced could be corrected in four days by the addition of solubilized liver or smaller amounts of more refined liver extract.

Studies on the liver concentrates have shown that the active constituent having this property was closely associated with "folic acid." Some evidence has been presented which suggests that it is similar to vitamin Bc an antianemic factor for the chick and at least one form of the *Lactobacillus casei* factor. A recent review of the literature concerning the relationship of folic acid vitamin Bc and the *Lactobacillus casei* factor has been prepared by Wieder (*44*).

Solutions of pure crystalline folic acid have been tested to determine if they have the capacity to correct the blood dyscrasia in a rat. The experimental results reported by Daft and Sebrell (*36*) indicate very

conclusively that "folic acid" does have this effect on such a leukopenia For example the administration of a solution of "folic acid" when given in a daily dose of 0 2 cc for four days was accompanied by an average rise in total leukocytes from 2700 per cubic millimeter to 14 000 per cubic millimeter and an average increase in the percentage of granulocytes from 1 to 39 per cent It appears to be definitely proven therefore that solutions of crystalline "folic acid" show activity in correcting the leukopenia and granulocytopenia in rats induced by feeding various types of sulfonamide drugs in purified diets

The Possible Relation of Vitamin Deficiencies to Agranulocytosis — One suggested explanation of the increased frequency of this condition is that a widespread "conditioning mechanism" may have been produced in a certain proportion of the inhabitants of this and other countries which may have rendered them susceptible to the action of certain drugs A possible clue to this perplexing etiologic riddle is the apparent increase in mild vitamin deficiencies especially those due to a decreased intake of the B complex which has been attributed to the changing dietary habits especially of the American people In three patients recently observed (45) who developed agranulocytosis following the therapeutic exhibition of sulfadiazine one had definite evidence of pellagra necessitating treatment Another had experienced a loss of 25 pounds of body weight as a result of an antiobesity diet a short time before the onset of the present illness The third was a male age 70 years about whom no information was available concerning his dietary habits It should be emphasized however that older persons frequently have a poor appetite and commonly have mild dietary deficiencies In addition this patient developed the agranulocytosis after a 28-day postoperative period following repair of a strangulated inguinal hernia During this interval his diet was very inadequate

This theory namely that a vitamin deficiency acts as a "conditioning mechanism" which causes persons to become more susceptible to the action of certain drugs known to cause agranulocytosis may explain some of the unusual aspects of the etiology of the disorder It is a plausible interpretation of the occurrence of agranulocytosis as a "new" syndrome because there is some reason to believe that at least mild degrees of vitamin deficiency are more prevalent now than previously Furthermore it offers a logical explanation of why some persons are sensitive to certain drugs causing this syndrome and others are not Some corroborative experimental evidence is available which lends support to this suggestion in the work of Day and his associates In 1940 (46) they reported that a leukopenia as low as 700 cells per cubic millimeter occurred in monkeys when they were fed the Goldberger black tongue producing diet

Further evidence previously cited in support of the vitamin deficiency theory is that sulfaguanidine and succinyl sulfathiazole have

been shown by Spicer (35) and his associates to produce agranulocytosis in rats It is accepted that these drugs act as intestinal antiseptics and that the B vitamins are synthesized in the rumen of herbivora Furthermore the agranulocytosis thus produced can be treated with whole dried liver and certain liver extracts and this curative effect may be associated with the vitamin content of these substances

Additional support of the theory that a possible vitamin deficiency may be concerned with the production of agranulocytosis is to be found in the study of Miller and Rhoads (47) These investigators observed the effect of feeding a modified Goldberger diet to dogs which resulted in their death from acute black tongue The terminal features were an ulcerative gangrenous stomatitis in which spiral and fusiform organisms were found leukopenia granulopenia and a suppression of maturation of the hematopoietic elements of the bone marrow It should be emphasized however that the leukopenia in this experimental condition differed from that of agranulocytosis in humans in at least two important respects First though pronounced in animals total or even almost complete granulocytosis was never observed And second in no instance did the decrease in circulating granulocytes precede the appearance of symptoms Examination of the bone marrow showed a cessation of the maturation of the granulocytes and this change was clearly the cause of the decrease in the circulating leukocytes There can be no question but what the changes as a whole have some resemblance to those occurring in humans with agranulocytosis

Agranulocytosis and Leukopenia Due to Thiouracil—In the original paper dealing with the effect of thiouracil on patients with toxic goiter Astwood (48) made clear that as the drug had never been administered to human beings previously possible toxic effects might be observed In fact among the first ten patients treated with this drug he observed the development of a non fatal case of agranulocytosis This patient a male age 37 years had experienced the symptoms of toxic goiter for three years After receiving thiouracil for 36 days in a dosage of 1 0 to 2 0 grams daily he developed severe pharyngitis with a body temperature of 105 degrees F The total white blood cell count was found to be 1000 per cubic millimeter and there were no granulocytes in the circulating blood for seven days After a critical illness during which time treatment with sulfathiazole liver extract and pentnucleotide was given the patient recovered

Since the original article by Astwood (48) others dealing with agranulocytosis have appeared and undoubtedly some cases have not been reported In a second article Astwood (49) states that agranulocytosis occurred in two patients in a group of 62 persons treated with the drug Of these 11 had normal thyroid function and 51 had toxic goiter This would give an incidence of 3 2 per cent It is reported

by Williams and Clute (*50*) that the complication occurred in one patient of the 72 treated or a frequency of 1 4 per cent In summarizing the treatment of 142 cases of toxic goiter of whom 135 were treated with thiouracil and seven with thiourea McCormack and his associates (*51*) found that agranulocytosis developed in two who were taking thiouracil and in one from thiourea This gives an incidence of agranulocytosis in three patients of the 142 treated or 2 1 per cent

In our own group of 36 patients treated with thiouracil in doses not exceeding 0 4 to 0 6 gram daily it was observed that in five the white blood cell count and percentage of neutrophils fell to the level of a leukopenia The lowest white blood cell count in the group was 2250 per cubic millimeter and the greatest reduction in the percentage of neutrophils was to 15 In only one of the patients however was there evidence of severe infection of the throat In two of the patients the condition was revealed only because routine studies were being made of the white blood cell count every other day in all patients receiving the drug in order to determine accurately the incidence of a leukopenia It seems fair to state however that in only 1 to 3 per cent of the patients who are treated with the drug there will be a *pronounced* fall in the number of granulocytes of the circulating blood which may or may not be associated with evidences of infection in the body usually in the mouth and throat

Fortunately in most instances after the drug has been omitted for several days the white blood cell count returns to normal and untoward symptoms when present have disappeared Recovery has not always occurred however for a fatal case is reported by Kahn and Stock (*52*) and Haler (*53*) makes the *unsupported statement* that thiouracil is a dangerous drug and at least a half dozen fatal cases of agranulocytosis have been described following its use" The case of an emaciated male with toxic goiter age 70 years who died of agranulocytosis following the administration of thiouracil is reported by Ferrer Spain and Cathcart (*54*) He was treated with 113 6 grams of thiouracil over a period of 128 days For the major portion of this time the dose was from 0 9 to 1 2 grams daily His white blood cell count was found to be 1250 with 37 per cent polymorphonuclears He died on the seventh day after the agranulocytosis was determined Just before death his white blood cell count was 450 per cubic millimeter and no granulocytes were present The only treatment mentioned was pentnucleotide intramuscularly and blood transfusions

I have no doubt but what other fatal cases have occurred but have not been reported Further data which have a bearing on the hazards of thiouracil therapy have been presented by Astwood On November 4 1944 at the regional meeting of the American College of Physicians in Chicago he stated that in the treatment of 6000 to 7000 cases of

been shown by Spicer (35) and his associates to produce agranulocytosis in rats It is accepted that these drugs act as intestinal antiseptics and that the B vitamins are synthesized in the rumen of herbivora Furthermore the agranulocytosis thus produced can be treated with whole dried liver and certain liver extracts, and this curative effect may be associated with the vitamin content of these substances

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by Williams and Clute (50) that the complication occurred in one patient of the 72 treated or a frequency of 1.4 per cent. In summarizing the treatment of 142 cases of toxic goiter of whom 135 were treated with thiouracil and seven with thiourea, McGavack and his associates (51) found that agranulocytosis developed in two who were taking thiouracil and in one from thiourea. This gives an incidence of agranulocytosis in three patients of the 142 treated or 2.1 per cent.

In our own group of 36 patients treated with thiouracil in doses not exceeding 0.4 to 0.6 gram daily it was observed that in five the white blood cell count and percentage of neutrophils fell to the level of a leukopenia. The lowest white blood cell count in the group was 2250 per cubic millimeter and the greatest reduction in the percentage of neutrophils was to 15. In only one of the patients however was there evidence of severe infection of the throat. In two of the patients the condition was revealed only because routine studies were being made of the white blood cell count every other day in all patients receiving the drug in order to determine accurately the incidence of a leukopenia. It seems fair to state however that in only 1 to 3 per cent of the patients who are treated with the drug there will be a *pronounced* fall in the number of granulocytes of the circulating blood which may or may not be associated with evidences of infection in the body usually in the mouth and throat.

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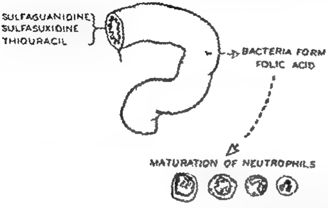

Fig 73 —This diagram illustrates a possible theoretical relationship between the action of certain drugs when taken orally and the development of agranulocytosis There is evidence to suggest that sulfaguanidine sulfasuxidine and thiouracil when taken by mouth will cause a reduction in the number of normal intestinal bacteria It is considered that these organisms are responsible for the synthesis in the intestines of folic acid which influences the rate of maturation or development of the granulocytes in the bone marrow With the diminution of bacteria and the resultant decrease in the amount of folic acid which is produced the rate of development of these cells and hence their emergence into the circulating blood is thought to decrease As it is likely that they continue to be destroyed at the normal rate the number in circulating blood must fall It is thought that this mechanism may explain why agranulocytosis develops in patients receiving such drugs especially thiouracil In two instances at the University of Michigan patients have developed agranulocytosis following the administration of sulfasuxidine While the above diagram illustrates a plausible theory it must be kept in mind that there are many gaps in our knowledge concerning the mechanism of the production of agranulocytosis and further study may alter the above concept completely

toxic goiter with the drug nine deaths had occurred This would give a mortality rate of approximately 0 2 per cent No statement was made concerning the cause of death in these cases but it would be a reasonable assumption that some have been due to agranulocytosis

It was hoped that when propylthiouracil replaced thiouracil in the treatment of toxic goiter that the untoward reactions would be less in number This is true and certainly this drug is the most satisfactory one at present to employ It may however occasionally cause reactions among them being agranulocytosis In reviewing the course of 672 patients who received this drug Bartels (55) noted that three developed agranulocytosis and in addition four a leukopenia The incidence of reactions of all kinds in the series including fever skin irritation dermatitis and changes in the white blood cell count was 1 6 per cent Those who developed agranulocytosis made up about 0 5 per cent Bartels (55) warns that propylthiouracil must be administered under careful supervision since serious reactions may occur following its use which require immediate treatment if complications are to be avoided On the other hand with care it is possible to employ this drug with safety Nevertheless a fatal case who failed to react to large doses of penicillin is reported by Julian and Harris (56) in 1949

The Cause of Agranulocytosis and Leukopenia in Patients Treated with Thiouracil—The fact that only a small per cent of patients who

receive thiouracil develop an important leukopenia or agranulocytosis at once suggests that certain individuals have an idiosyncrasy to the drug This is only a surmise however and is the usual present day theory suggested when only an occasional person reacts adversely to certain medications whereas others do not It has been suggested that the explanation may be that the dosage of the drug was excessive in those who develop this complication but this is not supported by the facts For example in surveying the reports in the literature it is found that important reductions in the numbers of white blood cells resulted from the administration of the following amounts of the preparation 83 grams in 35 days 39 grams in 36 days 30 6 grams in 54 days 16 0 grams in 21 days and 16 grams in 16 days In our own five cases the condition developed after the following amounts of the drug had been taken 4 8 grams in 12 days 7 2 grams in four days 28 8 grams in 79 days 7 2 grams in 18 days 32 8 grams in 142 days Many patients have received much larger doses without harmful effects

The possibility arises from the work of Goldsmith and his collaborators (57) that the reduction in the number of white blood cells results from a disturbance of the synthetic production of folic acid by the normal flora in the intestine It is suggested as has been previously emphasized by Hettig and Sturgis (45) that persons who have a vitamin deficiency might be more susceptible to the sulfonamides with a resultant agranulocytosis This same mechanism might also explain the occurrence of an occasional case resulting from the action of thiouracil

Methods of Prevention or Precautions to Take in Order to Protect the Patient from Developing Agranulocytosis Due to Thiouracil—Sufficient information has already been accumulated to indicate that thiouracil is a drug of great promise in the treatment of toxic goiter hence it is likely to be employed extensively in the future As agranulocytosis is a most serious complication which might prove fatal all measures should be instituted to prevent its occurrence It is the opinion of Astwood (49) that *the most reliable evidences of impending danger* from this source are the subjective reactions of the patient and the body temperature Although he concedes that frequent leukocyte counts are helpful it is his belief that leukopenia is not as reliable as the clinical symptoms which are indicative of the early onset of important complications According to him "Serious side effects could probably be avoided if the patients were instructed to seek medical advice as soon as abnormal symptoms were experienced"

One of the unexplained and remarkable observations in relation to agranulocytosis in this condition has been that the patients in most instances may resume taking the drug with immunity after the white blood cell count has returned to normal This is not always true however for one of my patients experienced a severe second attack

of agranulocytosis when the drug was resumed some weeks after the first episode of the disease

An acceptable explanation of the immunity to further attacks in a large percentage of cases has not been formulated up to the present time This is of interest in association with the observation that in agranulocytosis attributable to sulfadiazine patients have been known to make a complete recovery even though the likely causative drug is continued in full therapeutic doses (58)

It has been suggested by Goldsmith and his associates (57) that liver be fed or folic acid administered in the prevention and treatment of thiourea induced granulocytopenia This suggestion is based on the work of Spicer and his associates (35) also Kornberg *et al* (43) who demonstrated that the granulocytopenia induced in rats fed sulfonamides could be corrected by feeding liver It was shown by Goldsmith and his collaborators that the feeding of thiourea to adult male rats resulted in the development of a definite neutrophilic granulocytopenia which could be almost completely prevented by the feeding of solubilized liver Whether or not the administration of liver or other material containing folic acid will be effective in preventing the changes in the white blood cells following the use of thiouracil in the treatment of toxic goiter remains to be demonstrated It is however a rational suggestion supported by experimental observations and the results attained in humans may be well worth while

Treatment of Agranulocytosis Due to Thiouracil —It is emphasized by McGavack and his associates (51) that moderate leukopenia with a lymphocytosis may not necessarily be interpreted as evidence of toxicity due to thiouracil and hence such a change does not necessarily indicate permanent cessation of the therapy It does in my opinion make necessary the careful observation of the white blood cell count and either a reduction or preferably a discontinuance of the drug for a period of several days after which it can often be resumed without a recurrence of the leukopenia *This is not always true* however and when there is resumption of such therapy there should be careful observation of the patient including determination of the white blood cell count at frequent intervals

Further details concerning the treatment will be found in the section on page 1016 dealing with the therapeutic measures recommended for patients who have fully developed agranulocytosis

The Relation of the Barbiturates to Agranulocytosis —When it was first discovered in 1932 that this syndrome was related to aminopyrine suspicion was at once also directed to the possible role which various hypnotic drugs might play in its production This was due in large part to the fact that many drug houses marketed a preparation composed of a hypnotic drug usually a barbiturate in combination with

aminopyrine Often as in the case of allonal peralga and amytal compound and many others the name gave no indication of the presence of aminopyrine in the mixture In many instances no doubt the patient was unaware that aminopyrine was being taken It became clearly established that in some instances agranulocytosis followed the *ingestion of such preparations* and the *condition* was *attributed* incorrectly to the hypnotic drug rather than to the aminopyrine In general it may be said that the present day attitude is one which considers that the barbiturates or other hypnotic or sedative drugs rarely if ever cause the disease

There are a few convincing cases on record however in which it seems that drugs of this class were undoubtedly the responsible etiologic agent Plum (6) reports the case of a patient who had a rash with fever following the administration of phenobarbital (luminal) A week or so later when all evidence of this reaction had disappeared the patient was given 0.5 gram sodium diethyl barbiturate with 0 5 gram phenacetine Within 10 minutes a pruritic rash occurred and in the next few days there was a rise in temperature fever and stomatitis Four days later the white blood cell count was 1430 per cubic millimeter with 2.5 per cent granulocytes Death occurred the following day

The case of a woman age 37 is reported by Jackson (59) This patient had taken more than 38 liters of elixir of phenobarbital in the five years prior to the onset of the agranulocytosis in addition to an unknown quantity of phenobarbital tablets Although the patient undoubtedly had agranulocytosis and it followed the excessive use of a hypnotic drug there is no evidence that this drug was of etiologic significance in producing the condition Jackson expressed the view at this time that there was no convincing proof in the literature that hypnotic drugs alone especially the barbiturates will cause granulocytopenia although he recognized that many cases have been reported following the use of these drugs when combined with aminopyrine

There is one case in the literature in which agranulocytosis followed the use of the new formula for allonal This preparation had previously contained a mixture of aminopyrine and allurate but this was changed to allurate and acetophenetidin For this reason it was suspected that the patient was susceptible to allurate Following the administration of 0 07 gram of sodium allurate on two successive nights the patient developed a chill and fever the gums became sore and two white spots of exudate appeared in the tonsillar region Six days after the last dose of medication the leukocyte count was 1800 per cubic millimeter and no polymorphonuclear neutrophil cells were present This case report offers evidence that this particular type of barbiturate may be a causative agent Certainly proven cases are rare

Gold Preparations as a Cause of Agranulocytosis —Since gold thiosulfate was introduced into medicine in 1924 there has been an increasing

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Gold Preparations as a Cause of Agranulocytosis—Since gold thiosulfate was introduced into medicine in 1924 there has been an increasing

use of gold salts as a therapeutic agent in rheumatoid arthritis lupus erythematosus and various other diseases The earliest reports which indicated that this metal might cause agranulocytosis came from France where it was used in the treatment of tuberculosis Although it is now extensively employed in the United States for the treatment of rheumatoid arthritis *it is not common to learn of the development of* agranulocytosis as a complication Nevertheless on account of the serious nature of the disease one should always keep in mind the development of such a complication when using this therapeutic agent

The following information regarding the relationship between gold preparations and agranulocytosis has been accumulated *(60)* *In about* one half of the cases the interval between the initial injection of gold salts and the decrease in the polymorphonuclear neutrophil cells is 30 days *or less but it may be as long as six months* There is no evidence that one gold preparation is more likely to cause the condition than any other nor does the total dosage appear to be important According to Minck (60) agranulocytosis supervenes in about 1 case in 1000 in which gold salts are employed In approximately one half of the cases in which *it does develop the patients recover and in an equal number they* succumb Neither sex age underlying disease dosage of the gold salts the preparation employed nor length of time from the beginning of therapy and the appearance of the blood changes seem to make any difference in the prognosis

Arsenic as a **Cause of Agranulocytosis**—It has long been recognized that arsenic in the form of arsphenamine and neoarsphenamine may occasionally produce various types of blood disorders In 1932 Loveman *(61)* collected 59 cases from the literature which indicated that this drug could affect each element of the bone marrow namely the red blood cells the white blood cells and the platelets and that they could be involved singly or in combination He found in the 59 cases there were 30 cases of aplastic anemia with 18 deaths 14 cases of purpura hemorrhagica with five deaths and 15 cases of granulocytopenia with six deaths The term granulocytopenia was reserved by Loveman to include only those cases in which the polymorphonuclear cells alone were diminished

A number of cases of agranulocytosis are reported by Loveman in the article referred to above of which the following is a typical example indicating beyond the question of a doubt that typical agranulocytosis can result from the use of an organic arsenical preparation The patient was a 26-year old female who entered the University of Michigan Hospital with the chief complaint of sore throat and mouth The condition had appeared 10 days before her admission and 24 hours after her fourth weekly injection of neoarsphenamine for primary syphilis Her temperature had been elevated to 101 degrees F but there had been no chills or jaundice The patient appeared to be acutely ill The entire mouth

was inflamed and there were superficial ulcerations about the lips and tongue. The red blood cell count was 4.1 millions per cubic millimeter, the hemoglobin 80 per cent (Sahli), and the white blood cell count 600 per cubic millimeter; only one white cell was seen in 15 minutes examination of the stained smear. The patient succumbed 11 days after admission and necropsy showed the findings compatible with the diagnosis of agranulocytosis.

Twenty-four cases of leukopenia following the administration of salvarsan and neosalvarsan have been collected from the literature by Plum (6). Of the 47 cases, 38 were reported between the years 1932 and 1936. Often the arsenical preparations were given in combination with bismuth but Plum was unable to discover any difference between the cases treated with salvarsan or neosalvarsan and bismuth and with the arsenical preparations alone as far as the causation of agranulocytosis was concerned. In other words it did not appear likely that bismuth contributed to the production of the leukopenia. In 14 of the 47 cases he found that the hematological defect was limited to the granulocytes alone. Furthermore the physical examination revealed sore throat but no evidence of a hemorrhagic diathesis.

There does not seem to be any question therefore but what organic arsenical preparations may be responsible for pure agranulocytosis in some instances. In the opinion of Plum, however (6), the granulocytopenia induced by arsenic differs from the usual type in several particulars, some of which I do not consider to be of great significance. He did point out that the mortality was only about 30 per cent in the cases due to arsenic while the usual mortality from agranulocytosis due to other causes he claims is between 70 to 90 per cent, and that in the former the total white blood cell count tended to be higher. These differences have not been impressive in my experience.

There is some question as to whether inorganic arsenic may produce a reduction in the granulocytes of the circulating blood and the present day conclusion is that perhaps it may be responsible for such a condition but such instances are exceedingly rare. In 1925 Lawson, Jackson and Cattanach (62) reported 28 cases of inorganic poisoning and showed that such preparations may cause a pronounced reduction in the number of neutrophils in the circulating blood. In many of their cases, however, there was associated anemia and a hemorrhagic tendency. In 1928 Wheelihan (63) reported the case of a nine year old girl in whom the white blood cell count fell to 1300 per cubic millimeter with 3 per cent neutrophils following the administration of 0.41 gram of arsenic trioxide. In cases of lymphoblastoma and polycythemia it has been observed that the white blood cell count has decreased to a low level following the use of arsenic, but in my opinion this may have been due to the disease rather than the medication. In any event such cases cannot be considered to

be true examples of agranulocytosis My opinion concerning the relation of inorganic arsenic to the production of agranulocytosis is expressed clearly by Plum who says (6) So even though inorganic arsenic compounds are able in rare cases to produce leukopenia they do not appear ever to have given rise to Schultz s agranulocytosis

Presidon as a Cause of Agranulocytosis—*Presidon* is a polymorphous compound containing a pyridine nucleus, which has the chemical name of 3 3 diethyl 2 4 dioxotetrahydropyridine it is a mild hypnotic and sedative drug which is not a barbiturate As long ago as 1940 it was noted that the drug when given to rabbits caused a depression in the leukocytes (64) and also (65) when 600 milligrams was given daily to patients it caused a significant decrease in the white blood cell count In 1949, Tyson (66) reported a patient who developed a true case of acute agranulocytosis after ingesting 400 to 600 milligrams daily for two to three months The patient s white blood cell count fell to 3000 per cubic millimeter with a neutrophil percentage of 3 Similar cases have been reported by Ehrlich and Sussman (67) and by Covner and Halpern (68) As the drug has not had an extensive use and already this serious complication has been observed it does not seem wise to employ it as a hypnotic

Antihistaminic Drugs as a Cause of Agranulocytosis—Since the initial report of Clement and Godlewski (69) in March of 1945 it is clearly established that at least certain of the antihistaminic drugs can undoubtedly cause the classical syndrome of acute agranulocytosis These observers reported a case of agranulocytosis in a 13½ year old girl who was given for three weeks antihistaminic agent 2339 RP (N benzyl N phenyl N N dimethyl ethylenediamine hydrochloride) A number of patients have developed the disease after the use of tripelennamine (Pyribenzamine) hydrochloride (70 71 72 73) and one following the administration of a homologue of this drug Diatrin or methaphenilene hydrochloride In each instance the patients recovered due to the prompt omission of the drug and energetic treatment with antibiotic agents It should be stressed however that no patients should be given such antihistaminics without warning them that the manifestation of agranulocytosis might appear which calls for the prompt withdrawal of the drug and report for medical attention

Relation of Antiepileptic Drugs to Agranulocytosis—The dangerous side effects of the newer antiepileptic drugs have been reviewed by Abbott and Schwab (74) It is especially emphasized that Tridione (trimethadione or 3,5,5-trimethyloxazolidine 2 4 dione) and Mesantoin (3-methyl 5-phenyl 5 ethyl hydantoin) both anticonvulsants used in the treatment of epilepsy may produce among other toxic effects neutropenia and pancytopenia It has been noted by Davis and Lennox (75) in a study of 127 patients receiving Tridione that in 80 per cent there were no significant changes in the red blood cell count hemoglobin

platelets or the total white blood cell count Patients in this group apparently tolerated the drug in the usual antiepileptic doses for an indefinite period They may show a neutrophil count frequently below 50 per cent a corresponding increase in lymphocytes a reduction in monocytes and an increase in eosinophils The total white blood cell count however remains within normal limits Such a change would be termed by Davis and Lennox (75) as a *modified normal response* in which the total number of neutrophils is 3000 per cubic millimeter greater About 20 per cent of the 127 patients showed a total neutrophil count of less than 3000 per cubic millimeter and this group has been designated as a controlled neutropenia The change from the modified normal group to the controlled neutropenia group is gradual and may be detected usually by monthly blood examinations In a small per cent there is a further slow progression of the blood changes which may suddenly develop a clinical picture with dramatic explosiveness although probably the changes in the white blood cells the red blood cells and the platelets have progressed slowly Such a condition is a serious complication accompanied by bleeding tendencies (menorrhagia epistaxis petechia ecchymosis hematuria and gastro-intestinal bleeding) by severe infections and evidences of a severe anemia This condition usually terminates in death or if recovery occurs there is a prolonged convalescence

Mesantoin likewise produces at least some of the effects observed after the administration of Tridione

Streptomycin —The relationship of agranulocytosis to streptomycin is uncertain at present In the report on the effects of streptomycin on tuberculosis in man by the Council on Pharmacy and Chemistry of the American Medical Association (76) it is stated that there were eight instances of blood dyscrasias which appeared during the course of the treatment with this agent and five of these consisted of a relatively mild leukopenia with neutropenia In addition there were "three instances of agranulocytosis quite definitely due to streptomycin" They further state that although one of these patients had generalized miliary tuberculosis cessation of streptomycin therapy was followed by a return to normal of bone marrow function despite progression of the disease

A case of miliary tuberculosis in which agranulocytosis was observed is reported by Feld (77) A total amount of 76 grams of streptomycin was given over a period of 25 days The white blood cell count fell to 2700 cells per cubic millimeter and no neutrophil were present The drug was omitted and the patient became worse although the neutrophils returned in the circulating blood After an interval of 16 days the same daily dose (3 0 grams) was reinstituted but there was no return of the agranulocytosis This does not necessarily indicate that the patient had not been sensitive to streptomycin in my opinion because on repeated occasions this same resistance to a second course was noted in the

production of agranulocytosis with thiouracil in patients with toxic goiter It was the conclusion of Feld (77), in this case that the striking neutropenia was the result of the streptomycin therapy and not merely a consequence of the generalized tuberculosis—a conclusion which may be correct but difficult to prove

A pronounced leukopenia with neutropenia may occur in patients with tuberculosis who are not treated with streptomycin or any other preparation which may cause agranulocytosis It is reported by Pagel and Woolf (78) that in a case of fulminant tuberculosis septicemia the white blood cell count fell to 250 leukocytes per cubic millimeter although streptomycin was not given I have observed two patients both with fatal miliary tuberculosis before streptomycin was introduced into medicine who had white blood cell counts of 200 and 600 per cubic millimeter, respectively

The possibility that streptomycin may cause acute granulocytosis must be given serious consideration but it has not been proven beyond the slightest question of a doubt that this is true as tuberculosis may in its active and fulminating stages cause a similar picture

Relation of Chloramphenicol (Chloromycetin) to Leukopenia—It has *been reported by Volini and his associates (79) that the administration of* this antibiotic preparation may be followed by changes in the circulating blood and bone marrow Their observations were made on three cases of typhoid fever one complicated with amebiasis In one there was a profound anemia with a white blood cell count of 3200 per cubic millimeter with 8 per cent neutrophils in another there were no changes in the red blood cell count but the white blood cell count was 3000 per cubic millimeter with about 50 per cent neutrophils

It is difficult to prove that the observed hematological changes were due to the medication as they have been noted in patients with typhoid fever who were untreated I observed a fatal case of typhoid fever with a leukocyte count of 200 per cubic millimeter who did not receive any medication with drugs It must remain unproved that chloromycetin is responsible for such changes until further observations substantiate these claims

Agranulocytosis Due to Phenylbutazone—Recently a new drug phenylbutazone (butazolidin 3 5 dioxo 1 2 diphenyl 4 n butylpyrazolidin) having a structural similarity to aminopyrine has been introduced in the treatment of rheumatoid arthritis gout and other disorders This is known to have certain toxic effects as gastric irritation skin rashes fever and some degree of bone marrow depression The first case of true agranulocytosis as an untoward effect has been reported in 1953 by Hinz Lamont Havers Cominsky and Gaines (80) After their report had been submitted for publication they state that four similar cases have been published and references to these are given In the patient

reported by Hinz *et al* the white blood cell count was 500 per cubic millimeter with 4 per cent neutrophils and in addition there was a definite anemia with a red blood cell count of 3 0 millions per cubic millimeter and a hemoglobin of 8 4 grams per 100 cc (Sahli) This indicates that the drug affected the erythrocytes as well as the granulocytes Bone marrow aspirations showed absence of granulocytic forms and decreased erythrocyte formation The patient recovered following the use of ACTH and cortisone penicillin vitamin B_1 folic acid and injectable vitamin B (solu B) Bone marrow aspiration smears on the second day of hospitalization showed an absence of granulocytic forms and decreased erythrocyte formation

Pathogenesis of the Disease —A logical conception supported by convincing observations concerning the progress of the disease has been presented by Roberts and Kracke (51) It is their belief that the following steps occur (1) the earliest evidence of the condition is a change in the bone marrow with a failure of the myelocytic function which they consider may be due to myeloid aplasia or maturation arrest (2) after a few days there is a progressive diminution of granulocytes in the circulating blood until they may disappear entirely or number only a few hundred per cubic millimeter (3) the clinical onset with the appearance of the characteristic symptoms (4) with the loss of protection bacterial invasion occurs especially on the mucous surfaces and (5) the bacteria may enter the blood stream and cause death or the granulocytes may increase in numbers and exert their protective function with resultant recovery

Pathology —The most commonly encountered changes are the presence of necrotic lesions and bacteria in the various areas of the body parenchymatous degenerative changes in certain viscera and the alterations in the bone marrow (The latter are described on page 1112)

Changes in Various Organs —The spleen is usually enlarged to about three times its normal size and presents the features which are commonly observed in patients who succumb to a fulminating infection There is usually a striking engorgement with blood the lymph follicles are of small size there is an absence of granulocytes and occasionally small areas of necrosis are present There is no generalized swelling of the lymph glands but enlargement does occur as the result of logical drainage from necrotic areas This is most commonly present in the glands at the angle of the mandible Occasionally it is encountered in the mesenteric glands when the intestines are involved

Sites of Necrosis —The necrotic processes are secondary to the agranulocytosis but they constitute important clinical and pathological lesions in the disease The areas involved are most commonly the throat skin and digestive tract the frequency being in the order named In 30 cases Plum (6) found ulcerations in the throat in 28 The other two cases

showed merely swelling and edema of the mucous membranes He gives the sites of necrosis in the fauces, pharynx and larynx in 30 cases of agranulocytosis as follows

Tonsil	27 cases
Root of the tongue	17 cases
Sinus pyriformis	13 cases
Palatine arches	11 cases
Soft palate	9 cases
Entire pharynx	9 cases
Larynx	5 cases
Epiglottis	6 cases
Uvula	6 cases

In his experience not infrequently all of the lymphatic tissues of the pharynx were swollen and showed necrotic lesions In only three of the 30 cases were there necrotic lesions involving the esophagus stomach ileum jejunum, colon and rectum Occasionally the lesions may be present in the vagina

Plum (6) observed necrosis of the skin in about one third of his cases but this is rarely encountered as a complication in this country In my experience it has occurred only occasionally Plum lists the site of occurrence of the skin lesions in 24 cases as follows

Neck trunk and extremities	8 cases
Fingers toes and hands	6 cases
Lips	3 cases
Face (various parts)	4 cases
Nostril anus	1 cases
Eyelids	2 cases
Folds of skin	2 cases

The changes observed in the various viscera at necropsy are usually *not conspicuous The lungs commonly show congestion* and moderate edema In about one half of the cases there is an important pneumonia but aside from being bilateral and hemorrhagic there is nothing unusual about it Occasionally gangrene of the lung has been present In about 50 per cent of the cases the heart shows acute myocardial degeneration There are not infrequently parenchymal degenerative changes in the liver with some areas of central degeneration and vacuolation of liver cells *The organ is usually normal in size* The kidneys likewise show parenchymal degeneration which usually involves the convoluted tubules and the glomeruli

A very important finding in all fatal cases is that it is possible to grow bacteria of one type or another either from the heart's blood or from one or more organs of the body The bacteria most commonly encountered are *Streptococcus hemolyticus and non hemolyticus B Coli* Staphylococcus aureus B proteus and the pneumococcus

The Bone Marrow in Agranulocytosis —There has been some difference of opinion concerning the changes in the bone marrow in patients with

agranulocytosis All agree that there is a selective action on the granulocytic system of cells In most instances the mature granulocytes are absent while their precursors the premyelocytes and myeloblasts are observed in relatively large numbers In others only the myeloblasts remain as representatives of the white blood cell series The erythroblasts are normal in number as are the megakaryocytes

There is one point of difference however in the findings of various observers namely some report that there is a definite decrease in the number of nucleated cells whereas others consider that these cells are present in normal or even increased numbers As has been emphasized by Plum (6) it is likely that these differences can be reconciled when the alterations as shown by sternal puncture are considered in the different stages of the disease According to this observer all are in agreement as to the absence of mature granulocytes During the early or prodromal stages before changes are present in the peripheral blood he noted a complete loss of premyelocytes and almost a total absence of myelocytes and metamyelocytes in the bone marrow while the number of mature granulocytes was normal In another patient in the fully developed state when there was a complete absence of granulocytes from the peripheral blood just one day prior to death it was found that in the bone marrow there was almost a total lack of all granulated cells while myeloblasts were present in relatively large numbers Hence it could be said in this case that the formation of the granulocytes had ceased entirely and a true maturation arrest was present There was nothing in the bone marrow of this patient to indicate that regeneration was about to begin In a third patient who was in the beginning of the regenerative stage the peripheral blood showed 6 per cent granulocytes The bone marrow showed an early beginning of formation of granulocytes for not only were there myeloblasts but also premyelocytes present There were however no fully developed granulocytes The changes in the bone marrow therefore depend upon the stage of the disease in which the marrow is examined but the essential lesion seems to be as previously described by Fitz Hugh and Krumbhaar (13) one of maturation arrest of the granulocyte series

Symptoms and Signs —It is known that the reduction in the number of granulocytes occurs before the symptoms of the disease develop In an occasional patient however immediately after ingesting a causative drug such as aminopyrine there may be a chill and fever which must be interpreted as an immediate manifestation of sensitivity Unless further doses are taken the syndrome of agranulocytosis does not appear in such patients On the other hand with further dosage usually in the course of several days the patient develops the initial complaints which are known to precede the fully developed evidences of the disease

The earliest symptoms are lassitude malaise headache and a general

loss of the sense of well being These complaints are indicative of the onset of an infection and probably represent the time at which there is bacterial invasion involving the various mucous membranes of the body especially the mouth and throat Although the patient may have no other complaints the blood if examined at that time will often show a moderate reduction in the total leukocyte count with 50 per cent or less of the cells being granulocytes

As the disease progresses there is frequently a chill which may be an outspoken rigor, or merely a chilly sensation followed by a sharp rise in body temperature Although the early mental symptoms are mild they may become more pronounced as the disease progresses In many instances, even at the onset there is a profound sense of prostration which is out of proportion to the physical findings and change in the blood Some patients may remain lucid to the last but many become confused as high fever develops and outspoken delirium is not uncommon

By the time the chill has occurred and fever is present the infection is usually well established As a rule this is apparent from the complaints of sore throat and painful deglutition With progression of the disease the infection in the throat and oral cavity may become very extensive The mucous membranes of the fauces gums cheeks and sometimes the tongue are hyperemic swollen dry and frequently patches of brownish gray exudate are present which cover underlying ulcerations Usually the exudate is confined to the tonsils but in some seriously ill patients it may extend beyond and involve the palatine arches posterior wall of the pharynx uvula soft and hard palates oral mucosa and gums Necrosis of the tongue has been reported but it is rare and I have seen it in only one patient Other mucous surfaces in addition to the oral mucous membranes may be involved This is especially true of the areas at the junction of the skin and mucous membranes of the vagina and rectum

Necrosis of the skin may occur, but this complication I have observed only once This was in a fatal case in which superficial ulcerations developed in the inguinal region where there had been some irritation on account of an improperly fitted truss Plum (6) reports that skin involvement occurred in about one third of his cases

The skin lesions are described as beginning with a small red spot which develops into a bulla and on rupturing leaves a superficial ulceration Usually a limited area is involved but in rare instances the lesions have been reported as extensive

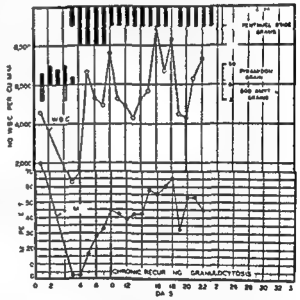
Mild to moderate jaundice is an important sign and is reported as occurring in about one half of the European cases While it has been noted in patients with the disease in this country it is not common and has never occurred in any patient I have observed with the disease Its presence usually indicates an extensive parenchymal hepatic change and hence an ominous outlook

There is no generalized lymphadenopathy but commonly there are moderately enlarged and tender glands in the neck or other regions which drain the area in which infection is present

Although the spleen is usually enlarged at necropsy it is almost never palpable during life Rarely is the edge of the liver felt below the costal margin but it may be in some cases in which jaundice is present

In about one half of the fatal cases the lungs show evidence of bronchopneumonia which is a common cause of death especially in the older patients

Fig 74 —This patient had experienced a number of attacks of agranulocytosis over a period of several years which were eventually discovered to be due to aminopyrine taken for the relief of dysmenorrhea The above chart shows the changes in the blood during one of these attacks As this was before it was known that aminopyrine could cause the condition she was actually given this drug as an antipyretic during her illness It will be noted that there was a prompt drop in the neutrophils following its administration Fortunately the patient complained that the aminopyrine made her uncomfortable For that reason it was discontinued and her recovery followed Although the patient received pentnucleotide it was probably of no benefit The patient also received sodium amytal but there is no evidence to indicate that this drug can cause agranulocytosis



Changes in the Blood —The most characteristic feature of this disorder is the remarkable decrease in the total white blood cell count which is mainly due to the striking reduction in the number of granulocytes In most instances the white blood cell count varies between 1000 and 3000 per cubic millimeter when the patient is first seen The lowest total level observed by me was one of 150 per cubic millimeter A count of 50 per cubic millimeter has been reported by Fitz Hugh and Comroe (82) The most impressive change in the blood is the amazing reduction in the actual numbers of granulocytes which are usually present in numbers varying from 20 per cent to none at all In Plum s (6) series of patients and in the remaining 10 per cent only a small number of these cells were present (1 to 2 per cent) I have found it a useful observation that the diagnosis of agranulocytosis should be questioned unless the per cent of granulocytes is below 50 regardless of how low the total white blood cell

count is found to be . Almost always the percentage of these cells is 20 per cent or less

In a great majority of cases there is a reduction in the total white blood cell count and the percentage of granulocytes as well but this is not always true If it were one could feel safe in doing only the total leukocyte count in any given patient who was receiving a drug which might cause the condition While the presence of a normal white blood cell count is usually a fairly good safeguard against the presence of the disease it is not an absolute guarantee that the early changes of agranulocytosis might not be present In one of my patients although no symptoms were present the polymorphonuclear neutrophil cells fell to 13 per cent at a time when the white blood cell count was 12 500 per cubic millimeter This occurred after he had received a large amount

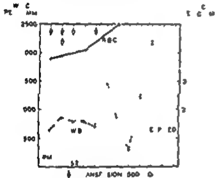


Fig 75 —The blood changes in an adult male admitted in a semi conscious condition with a body temperature of 102 degrees (F) are shown in the Fig He was found to have a palpable spleen a white blood cell count of 600 per cubic millimeter with 74 per cent neutrophils and a red blood cell *count of 3 9 millions per cubic millimeter* An admission diagnosis of agranulocytosis was made but no causative agent could be found Furthermore the enlarged spleen was against the diagnosis as was the high percentage of neutrophils (74%) A sternal puncture showed an increase in the number of primitive granulocytes and this lead to the diagnosis of subleukemic leukemia . At necropsy the patient was found to have miliary tuberculosis with an extensive involvement of the spleen

of succinyl sulfathiazole and when no symptoms which would make one suspicious of agranulocytosis were present

Although the condition is characterized by a sharp diminution in the number of granulocytes of the peripheral blood there is also often a decrease in the number of other white blood cells This of course is obvious from the fact that the total leukocyte count may be only a few hundred per cubic millimeter or even less than this The lymphocytes are commonly below the normal of actual numbers of 2000 to 3000 per cubic millimeter and are usually less than 1000 The monocytes are frequently much lower than the normal number of 200 to 500 per cubic millimeters It has *not* been my experience that the presence of a normal number of monocytes is necessarily a good omen from the standpoint of prognosis as others have claimed (83)

One striking fact about the blood in this disease is the selective action of the causative agent on the white blood cells especially the granulocytes Usually there is no important alteration in the red blood cells the

hemoglobin the size of the cells or color index Occasionally I have observed the red blood cell count to be in the vicinity of 3 8 to 4 0 millions per cubic millimeter and the hemoglobin to be correspondingly slightly reduced It is entirely possible of course that a patient with some type of anemia which is already present might develop agranulocytosis from an entirely unrelated cause

Another useful observation in diagnosis is that the platelets in agranulocytosis are almost always normal in number This is helpful in differentiating it from the subleukemic type of acute leukemia in which the platelets are often reduced in numbers

Differential Diagnosis —The following diagnostic criteria are of value in differentiating it from other conditions

1 Rarely are infants affected the disease usually occurs in adults between the ages of 25 and 60 years The apparent immunity of children and infants in the past has probably been due to the fact that the therapeutic agents which commonly cause the condition are not ordinarily given to children Now that it is known that the sulfonamide drugs may be responsible for it younger persons may be more commonly affected

2 Agranulocytosis is ordinarily a brief illness with an acute onset

3 There is almost always a pronounced leukopenia due primarily to a striking decrease or complete absence of the granulocytes from the circulating blood If not entirely absent they frequently comprise only 10 per cent or less of all white blood cells

4 There is no significant anemia or thrombocytopenia or a hemorrhagic tendency or at the most more than an occasional immature white blood cell in the peripheral blood These observations are important because in acute leukemia all of the four changes which have just been stated are commonly present

5 There is no enlargement of the spleen or liver on physical examination The lymph glands show no involvement except that sepsis may cause an increase in size and tenderness of the regional glands most frequently in the neck

6 Usually in true agranulocytosis it is possible to obtain a history of the use of some drug known to cause the disease A statement to the contrary causes one to question the accuracy of the information obtained

7 In almost all instances necrotic areas of the mouth throat and mucous surfaces are present This of course also occurs in aplastic anemia leukemia states diphtheria Vincent s angina various types of stomatitis and other infections Rarely is it present in overwhelming or generalized sepsis with leukopenia and hence aids in the differential diagnosis from such a condition

8 Sternal puncture is of assistance in differentiating the disorder from subleukemic leukemia aplastic anemia and other blood dyscrasias It should be emphasized however that the process of maturation arrest in

the bone marrow characteristic of agranulocytosis, may simulate the changes observed in some cases of acute leukemia

Further data relating to various conditions which may cause a leukopenia and hence be confused with agranulocytosis are given in the chapter on *Changes in Leukocytes (page 742)*

Prognosis and Treatment —Agranulocytosis must be regarded as a serious disease in which the outlook is always ominous The early statistics indicated that the mortality rate was about 75 per cent With the elimination of the causative drug however and the early application of the modern treatment the death rate should be 10 per cent or less The high mortality among the early cases was before it was known that the disease was usually due to a drug sensitivity and prior to the introduction of effective methods of treating the complicating and often lethal sepsis with sulfonamides and antibiotics The grave outlook in the early cases *is shown by the following statistics In Plum s series (6) of 88 patients* reported in 1937 the mortality rate was 88 per cent According to Jackson and Tighe *(84)* the death rate was 73 per cent in a group of patients who received no treatment or were treated inadequately The early cases which I saw between the years 1930 and 1933 in many instances had a rapid course and died within a week Usually the disease had become well established in these patients when first seen that is the white blood cell count was often below 1000 per cubic millimeter and sometimes was only a few hundred and the granulocytes of the circulating blood were less than 10 per cent and in some cases they were completely absent The *lowest total white blood cell count which I observed was 150 per cubic* millimeter In association with these blood findings there was usually a massive infection of the mouth and throat and death often resulted within a few days from sepsis or pneumonia When first observed the cases were far advanced and our knowledge of the disease was so incomplete at that time that the causative drug was not always eliminated Furthermore the sulfonamides and antibiotic agents were not available for combating sepsis *which was the most common cause of death*

Among the forms of treatment which have been suggested are the following blood transfusions of normal blood or from a patient with myelogenous leukemia stimulating doses of roentgen ray parenteral liver extract pentnucleotide adenine sulfate "leukocytic cream yellow bone marrow and vitamins including folic acid and pyrodoxine In my experience and I believe that most observers are in accord with this opinion at present *all of these preparations are now regarded as having* doubtful value and hence their use is not recommended It must be granted however that therapy in this disorder is difficult to evaluate In the past at least the patients were often *in extremis* when first seen unknown to the observer recovery may have followed omission of the offending drug In many instances several forms of treatment were

administered simultaneously so it was difficult to determine if improvement was due to any certain one or if it were spontaneous Finally cases of acute agranulocytosis are rare and hence it was not possible for any one observer to obtain reliable and firsthand information on a large group of patients The condition has never been reproduced in animals and hence the results which might be obtained from the experimental production and control of the disorder are not available

Sufficient experience has now accumulated however to indicate in my opinion that the *following therapeutic measures are to be recommended* If the patient is not in a state bordering on a terminal one when treatment is first instituted and the following measures are carried out efficiently it is my estimate previously stated that less than 10 per cent will succumb The remainder will make a complete recovery although some may have a prolonged convalescence Recommended measures

1 Prohibition of the causative drug

2 The energetic treatment of sepsis with antibiotic agents In patients who are severely ill I would recommend 4 million units of penicillin intramuscularly daily and 0 5 gram of aureomycin intravenously in 500 cc of salt solution twice daily It is recommended that these measures be continued until the body temperature has been normal for at least three days Undoubtedly in the future even more effective methods of employing the antibiotic agents and newer preparations will be available At the present writing however the above method has proved to be an efficient one

3 General measures including an adequate fluid intake either orally or intravenously and local treatment of the infected areas with dilute solution of hydrogen peroxide

The administration of liver extract and folic acid parenterally may be tried but they are not regarded as having sufficient beneficial effect to be recommended

Blood transfusions have been recommended on the basis that the total white blood cell count may be increased As pointed out by Dameshek (4) when 500 cc of blood is removed from a donor with a white blood cell count of 10 000 per cubic millimeter and this is given to a person with a normal blood volume of 5000 cc the total rise in leukocytes would be 1000 per cubic millimeter Of these no more than 70 per cent would be granulocytes which probably would not survive more than a few hours Theoretically the procedure does not seem to be worth while and experience has not demonstrated that blood transfusions have been an effective therapeutic agent in this condition

It has been recommended by Bock (85) and by Rybakov (86) that patients with myelogenous leukemia be employed as donors for patients with agranulocytosis Dameshek (4) has calculated that if the blood for transfusion be obtained from a donor with myelogenous leukemia and a

white blood cell count of 200 000 white blood cells per cubic millimeter and that 500 cc is given the recipient should have an increase of about 20 000 per cubic millimeter There are however objections to this procedure which make it an unlikely form of therapy In the first place it is not easy to obtain a patient with *untreated myelogenous leukemia* who would be available for service as a donor Second it is probably true that a great majority of the white blood cells from a patient with this disease are inactive in the defense mechanism of the body for which purpose they are transfused And finally the remote possibility exists that the transfusion of blood from a patient with leukemia is not an entirely safe procedure despite the few experiments which so far have indicated that the disease in humans is not transmitted by blood transfusions

Usually when the disease subsides recovery is complete In one of our patients tracheotomy was necessary but ultimately this healed without complication when breathing was possible through normal channels One instance of esophageal stricture following agranulocytosis due to sulfonamide therapy is reported by Bryan (87) This complication necessitated a transthoracic esophagectomy with complete relief of all symptoms except mild indigestion following large meals

Prevention of Agranulocytosis —The prevention or the early treatment of agranulocytosis is of great importance for if the disease is recognized before it becomes well established the chances for a cure are much greater It is not practical however to depend on doing white blood counts two or three times weekly or even daily as a means of prevention The use of serial leukocyte counts in the prevention of agranulocytosis has been reviewed by Young (88) who concludes that there is no evidence to indicate that during the administration of agranulocyte producing drugs they will either prevent agranulocytosis or reduce case mortality In fact he believes that reliance on leukocyte counts is unreliable and may give rise to a false sense of security The reason for this he believes is because the condition may become fully established before the peripheral blood gives warning

In my own experience especially when giving thiouracil and related compounds it has been sufficient to warn the patient that a drug is being taken which might possibly cause untoward symptoms such as chills fever a skin rash or sore throat If any of these occurred he was advised to stop the drug immediately and report to a physician for a white blood cell count If the granulocytes are reduced to such a point that they are thought to be responsible for the symptoms present then intense treatment should control the condition

Chronic Agranulocytosis —Five cases with a persistent leukopenia have been classified by Adams and Witts (89) as having chronic agranulocytosis This condition they state is characterized by a persistent neutro

penia the white blood cell count being constantly below 4000 per cubic millimeter and the neutrophils below 1500 per cubic millimeter The only other characteristic of the condition is a tendency to recurrent infections "agranulocytic infections" as they term them occurring at irregular intervals These patients have no evidence of hemolysis no deficiency of iron or liver and no leukemic or other infiltration A mild degree of anemia is present but the condition may be differentiated from aplastic anemia because the patient with chronic agranulocytosis rarely requires blood transfusions whereas those with aplastic anemia frequently need such a form of therapy In separating this group of patients the authors considered that they had excluded aplastic anemia liver and iron deficient anemias leukemia other reticuloses splenomegaly and hemolytic anemia

The total white blood cell counts in these patients averaged between 2000 and 3000 per cubic millimeter and the total number of granulocytes between 308 and 1260 per cubic millimeter The red blood cell count was usually normal or not less than 3 6 millions per cubic millimeter

The course of the disease according to Adams and Witts (89) was characterized by a series of severe infections arising spontaneously or from trivial causes They included infections of the oral cavity throat severe infections following dental extractions otitis media septic fingers cutaneous infections suppurative lymphadenitis urinary infection septicemia, and unexplained fever

The intervals between the attacks differing sharply from cyclic agranulocytosis ranged from a few days or weeks to six years In the interim between the episodes the patients had fairly good health although they experienced ease of fatigue and weakness The average duration of the illness in the four survivors of the five patients studied by Adams and Witts (89) is now more than 5 years and the patients have shown no evidence of progressive deterioration

It is contended that these patients constitute a separate group and as an entity they can be designated chronic agranulocytosis There is no evidence of overactivity of the spleen as the spleen is not enlarged there is no indication of increased activity of the spleen as shown by increased blood destruction and splenectomy in one of their patients was not followed by improvement

It is considered by Adams and Witts (89) that the condition is *probably a variant of aplastic anemia* although it differs from this disease in that only one of the five patients died in an average period of five years and the sternal marrow is not so frequently hypoplastic as in chronic aplastic anemia Furthermore the anemia is much milder in chronic agranulocytosis rarely requiring blood transfusions a situation differing strikingly from that which usually prevails in aplastic anemia

Treatment and Prognosis—These patients do surprisingly well" according to Adams and Witts without splenectomy unless the attacks of

agranulocytosis are frequent, and unless the marrow is shown to be cellular in several situations, namely the vertebral spines and the iliac crests as well as the sternum. *The only form of therapy known to be of* benefit in such patients is the use of antibiotics when the attacks of infection occur.

Periodic (Cyclic) Neutropenia.—This is a rare condition, most commonly present in infants or young persons, characterized by episodes of granulocytopenia in association with gingivitis and aphthous ulcers in the mouth, fever, localized lymphadenopathy, and a remarkable tendency to recur regularly at intervals of three to four weeks. The literature has been reviewed and 16 cases collected by Reimann and deBerardinis (*90*).

Clinical Course.—*I have observed two patients with this disorder*, one a girl age 15 years who had experienced attacks since the age of 10 years. These occurred at approximately four week intervals. During these periods of acute illness aphthous ulcers and gingivitis were present, the white blood cell count was known to fall as low as 1200 per cubic millimeter and the granulocytes to 9 per cent. No other important changes in blood were apparent. The constitutional symptoms in this patient were mild. In another patient, a boy of 15, there was a history of similar attacks extending back for four years and occurring at intervals of three to four weeks. During one of the episodes which I observed, the temperature rose to 102 orally and the white blood cell count was 2400 per cubic millimeter with 10 per cent neutrophils, 2 per cent basophils, 5 per cent eosinophils, 15 per cent large lymphocytes, 21 per cent small lymphocytes, and 44 per cent monocytes. A few days before, the red blood cell count had been 4.7 millions per cubic millimeter, the hemoglobin 11.3 grams per 100 cc. of blood, and the platelets were slightly increased in number. There was moderate prostration when the acute symptoms were present. It is remarkable that despite these repeated attacks both patients appeared to be in reasonably good general health.

In studying the clinical course of a patient, a male, age 23, who had typical attacks about every two weeks for a period of five years, Owren (*91*) gives an excellent clinical description of a typical attack as follows: a day or so before the rise in body temperature the patient observes the premonitory manifestations of the approaching relapse in the form of fatigue, anorexia and irritability. Simultaneously or a little later scattered shallow ulcerations appear in the mucosa of the mouth and these follow the course of the ordinary apthous ulcers, becoming covered with grayish white sloughs surrounded by a red halo and in some instances developing into deep ulcerations accompanied by regional involvement of the lymph nodes and fever. The ulcerations are usually confined to the throat and oral cavity and are often associated with a pronounced gingivitis. Sometimes the relapses were associated with vesicular lesions progressing to necrotic ulcerations of the skin of the face, the anal regions and the extremities. A number of the attacks were associated with conjunctivitis

As the episode subsided the ulcerations healed with amazing rapidity The granulocytes decrease several days before the symptoms appear and progress to the point of severe granulocytopenia or a complete absence of granulocytes from the peripheral blood This phase of the blood change usually persists from three to five days

Bone Marrow —The bone marrow in the patients reported by Reimann and de Berardinis (90) repeatedly showed granulocytic hypoplasia during the episodes Between these times the marrow was normal but changes preceded those in the blood In Owren s patient (91) during the agranulocytic stage a promyelocyte myeloblastic marrow was present with almost a total disappearance of the mature forms Immediately before the increase in the granulocytes of the circulating blood the marrow showed a rapid increase of the more mature forms of granulocytes with a relative reduction of the promyelocytes and myeloblasts

Etiology —The cause of this disorder is completely unknown On account of the remarkable constancy of the attacks which occur at such regular intervals the possibility of some endocrine disturbance has been considered There is no conclusive evidence of this however as they occur in both males and females and they have been observed in infancy and after the menopause One patient is reported in which the attacks continued throughout pregnancy (92)

Although the recurrent attacks of cyclic agranulocytosis resemble those of acute agranulocytosis there is no evidence that the chronic forms are associated with sensitivity to a drug Furthermore it has not been possible to establish that the condition is due to a recurring infection or to the absence of a substance which is concerned with maturation of the granulocytes It appears logical to assume that the infection complicating the condition is secondary to the decrease in granulocytes It is suggested by Owren (91) that the condition may be explained on an allergic basis for as he says allergic diseases are frequently characterized by repeated attacks with free intervals despite the fact that the action of the allergin is continuous This could be explained on the basis that the allergic reaction is associated with neutralization of antibody which is followed by a period of freedom from anaphylactic reaction

Treatment —Treatment seems to be of no avail with the possible exception of splenectomy According to Reimann and de Berardinis (90) in four of six cases collected from the literature splenectomy induced an amelioration of the symptoms or a less striking diminution of the neutrophils or both In the remaining two cases however no benefit followed In a case studied extensively by Owren (91) splenectomy was also ineffective as was all forms of treatment which has been applied in acute agranulocytosis namely roentgen irradiation nucleic acids liver extracts vitamins and blood transfusions This observer emphasizes that the *secondary infection* may be controlled by the administration of *antibiotics*

and sulfonamides, although such treatment does not prevent or control the blood changes

Primary Splenic Neutropenia—In 1939 Wiseman and Doan (93) reported that they had encountered a syndrome consisting of granulocytopenia which they *considered to be similar to congenital hemolytic jaundice* or thrombocytopenic purpura in that the spleen according to their interpretation segregates and destroys leukocytes instead of red blood *cells or platelets* Such a condition was reported by them as occurring in the acute subacute and chronic forms They considered that they *had established the mechanism by sternal puncture* which revealed in each instance myeloid hyperplasia of qualitatively normal cells by splenomegaly *with profound peripheral granulopenia by the elimination* of Banti s syndrome chronic infection, and other contributing organic drug or environmental factors, and finally by the therapeutic test as shown by the beneficial effects of splenectomy This operation was followed by the prompt re establishment of a normal peripheral white blood cell count Histologically the spleen from three of the patients showed extreme clasmatocytosis with excessive phagocytosis of granulocytes

Three years later these same observers (94) reaffirmed their previous observations and suggested that the condition be termed *essential or primary splenic neutropenia* They believed the evidence indicated that the basic cause of the condition was an overactivity of the spleen which they called *hypersplenism,* in which there was *accelerated destruction* of the granular leukocytes of the peripheral blood by the reticulo *endothelial cells of the spleen*

The *diagnosis* of primary splenic neutropenia according to Wiseman and Doan (94) is based on the following clinical and hematological data splenomegaly occasionally purpura depending on the degree of associated thrombocytopenia sometimes oral ulceration which bears a direct relationship to the acuteness and severity of the neutropenia rarely mild icterus depending on the severity of the associated anemia The bone marrow *shows hyperplasia of the myeloid series and if the hemolytic* anemia is sufficiently severe also of the erythroid series but no abnormal cells are present and *there is no evidence of leukemia* *Examination of* the blood characteristically shows a pronounced specific neutropenia with a *white blood cell count often of 1000* per cubic millimeter or less and a granulocyte per cent which may be less than 10 per cent an anemia when present of the macrocytic normochromic type a reticulocytosis if a significant anemia is present an increased indirect van den Bergh depending on the severity of the anemia and a variable degree of thrombocytopenia

In general it is their conclusion that the presence of a palpable non tender spleen is the most important diagnostic criterion If this is present along with a severe neutropenia a variable but often slight anemia and

thrombocytopenia and if the bone marrow displays a hyperplasia of all elements without maturation arrest or pathological alterations the diagnosis in their opinion is sufficiently certain to justify the therapeutic test of splenectomy. Although undoubtedly the presence of a palpable spleen is of great diagnostic assistance the diagnosis must be considered when the organ cannot be felt. It is well recognized that the spleen must be several times as large as normal before it is palpable. Enlargement can usually not be demonstrated in patients with idiopathic thrombocytopenic purpura considered by some to be a form of hypersplenism and in my opinion its absence cannot eliminate the diagnosis of primary splenic neutropenia. This opinion is concurred in by Kracke (95) who says "not every case of hypersplenism is accompanied by enlargement of the spleen."

It is emphasized by Kracke (95) *that the epinephrine* test is an important measure in the diagnosis of hypersplenism. Caution should be used however in accepting this test either as confirmatory of the condition or in eliminating it from consideration. The technic of the test as described by Kracke is as follows. The test is done in the morning with the patient under basal conditions and after a rest in a reclining position of thirty minutes. During this time two complete blood counts including a differential are made. The patient is then given 0.5 to 1.0 cc of 1–1000 solution of epinephrine subcutaneously and the counts repeated at intervals of 10 minutes for one hour. The outline of the spleen is marked off and the blood counts are continued at 20 to 30 minute intervals until the spleen has returned to its original size. It is stated by Kracke (95) that they have not noted changes in the platelet count in patients with thrombocytopenic purpura furthermore a positive reaction is not elicited in familial hemolytic icterus. It does not appear therefore that the epinephrine test is sufficiently trustworthy to be of great diagnostic aid. According to Dameshek and Estren (96) the adrenalin test has not been helpful in their hands their criticisms being that adrenalin acts on the nodes marrow and liver as well as on the spleen the results may be the same after as before splenectomy and the mechanism of the results are uncertain.

The disorder may resemble superficially Banti's syndrome Felty's syndrome subleukemic myeloid leukemia hypoplastic anemia agranulocytosis and the reaction to certain types of chronic infection. For a more detailed description of hypersplenism reference should be made to the section dealing with this condition on page 182.

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The increase in the total number of red blood cells as a basis for symptoms did not at first receive general acceptance In fact Hayem (6) in his treatise on hematology makes the flat statement that "I do not believe in the existence of a plethoric state which can be ascribed to an increase in the red cells"

In 1889 Cuffer and Sollier (7) described two cases which were undoubtedly polycythemia as seen today Reference to this publication was made by Vaquez in his original description of the disease He emphasized that the manifestation of the condition correspond exactly with the symptoms observed in his cases Unfortunately Cuffer and Sollier did not determine the number of red blood cells

The original clinical description of polycythemia vera complete in all details including a careful examination of the blood must be recognized as that of Louis Henri Vaquez (8) which appeared in the year 1892. In this article he makes reference to the fact that the red blood cells may be increased by a stay at high altitudes in cardiac patients and in patients with cholera following the rapid loss of fluids from the body thereby concentrating the blood In describing his patient who had a red blood cell count of 8 900 000 per cubic millimeter with "the white cells remaining practically normal" he emphasized among other matters the fact that polycythemia can be persistent not always transient and that it can account for a definite group of symptoms His patient was a 40-year-old male who had a constant bluish cyanosis an overdistention of the superficial veins dyspnea and palpitation Furthermore he complained of vertigo tinnitus vague digestive disturbances and bleeding of the gums Vaquez summarized the clinical picture of his patient in the following classical words "We are dealing with a man afflicted with chronic cyanosis without a trace of edema with a considerable dilatation of the veins with an intense redness of the face marked injection of the conjunctivae the whole caused probably in the absence of any other plausible hypothesis by a congenital lesion of the heart which in any event does not give any certain sign on auscultation" Along with these findings the liver and spleen were also found to be enlarged

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CHAPTER XX

POLYCYTHEMIA

Introduction.—The term polycythemia has been employed as a general one to indicate a significant increase in the red blood cell count above normal limits. According to Harrop and Wintrobe (*1*), the upper limit would be 6.2 millions per cubic millimeter for men and 5.4 millions in women. Bethell (2) found that in the vicinity of Ann Arbor 95 per cent of all red blood cell counts in men ranged between 4.7 and 6.0 millions per cubic millimeter with an average of 5.35 millions per cubic millimeter and in women between 4.13 and 5.21 with an average of 4.67 millions per cubic millimeter.

The standard values for the red blood cell count as given by the United *States Air Force Technical Report No. 6039* are as follows: for men, 5.4 with a range varying from 4.6 to 6.2 millions per cubic millimeter. For women the average is given as 4.8 with a normal range of 4.2 to 5.4 millions per cubic millimeter.

History.—Although earlier references had been made to what might have been examples of true polycythemia, it was not until the actual enumeration of the red blood cells was done in patients with the disease that it could be identified with a certainty. As early as 1757 Alberto von Haller, a Swiss scientist, made the statement that (3) a plethoric or sanguine habit arises from an abundance of red blood cells and further more "seeing the curor deprived of its watery part congeals and obstructs the smallest passages of the vessels and kindles too great a heat." The interpretation of this sentence by Dreyfus (*4*) is to the effect that it may be the first claim of thrombosis with gangrene occurring in the course of polycythemia. Although Haller examined the blood, he apparently did not attempt to estimate the number of erythrocytes.

In 1884 Gabriel Andral included a chapter dealing with an excessive number of erythrocytes in the circulating blood in his brief monograph on blood diseases (5). This observer in discussing patients with plethora states that some have no important symptoms whereas others are observed to have vertigo, tinnitus aurium, cardiac palpitation, excessive difficulty of respiration, and injection as though apoplectic of the conjunctivae of the eyes and of the face, etc. He concludes that the "blood of plethoric persons then differs from ordinary blood in the greater quantity of globules and much less quantity of water it contains.

The increase in the total number of red blood cells as a basis for symptoms did not at first receive general acceptance. In fact Hayem (6) in his treatise on hematology makes the flat statement that "I do not believe in the existence of a plethoric state which can be ascribed to an increase in the red cells."

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(about) in whom the chief clinical manifestations were cerebral Necropsy showed a small hemorrhage of the middle meningeal artery and *passive congestion of all organs* One week after this publication appeared he reported at the Clinical Meeting of the Medical Board of the Massachusetts General Hospital (*11*) the details of a second case which *he had observed* In this patient the red blood cell count was 12,000 000 per cubic millimeter He ventured the opinion that in such conditions "we are not dealing with a genuine plethora but a venous congestion the cause of which however remains a mystery In June 1901 Sylvester F McKeen (*12*) also of Boston published the details concerning a second case with a red blood cell count of 9,840 000 per cubic millimeter which showed that Dr Cabot s case reports had evidently aroused interest in the disease in the vicinity of Boston, and that the condition was not so rare

The papers by Wilhelm Turk published in 1902 and 1904 (*13, 14*) were of great importance as contributions to our knowledge of polycythemia although they have been overlooked to a certain extent by the general medical profession His most significant observation was based on a careful study of the changes in the circulating blood in which he *noted that there was not only a pronounced increase* in the hemoglobin and red blood cells but also that there was an excessive number of white blood cells Furthermore he observed immature white blood cells and *red blood cells in the circulating blood* *He also pointed out* that microcytes poikilocytes and achromic erythrocytes may also be present His findings suggested to him that these changes were indicative of a hyperactivity *of the myeloid system as well as the red blood forming* elements in the bone marrow He considered that the disease might be due to a primary hyperplastic condition of the erythroblastic myeloid tissue, and *he first proposed the name erythremia or erythrocythemia* The article written by Turk in 1904 (*14*) has a complete bibliography of the scientific articles dealing with the subject up to that time

Osler s initial publications on polycythemia first presented before the meeting of the Association of American Physicians in May 1903 attracted *the attention* of the medical world especially the English speaking part of the medical *profession to this disease more than any other* publication dealing with the topic (*15 16 17*) He discussed in accurate detail all of the significant clinical manifestations of the condition with especial emphasis on *the classical symptoms the cyanosis and* congestion of the vessels of the conjunctivae the headache vertigo weakness and prostration and the "torpor mental and physical Special *mention* is made of the blood *examination* and a *review of these changes* as noted by other observers is given He concludes his article written in 1903 with the statement that our knowledge concerning the disease is imperfect and suggests (1) a careful study *of all forms* of polycythemia especially those

of a secondary nature (2) a more detailed study of the blood in these patients especially the volume viscosity the amount of hemoglobin the specific gravity and the diameter of the corpuscles It was his suggestion that "an increased viscosity of the blood with resulting difficulty of flow" seems the most plausible explanation of the cyanosis and (3) a careful investigation of the relation of the splenomegaly to the cyanosis and polyglobulism His final sentence terse and to the point is so characteristic of Osler that it is recorded verbatim It is as follows "Future investigation will determine whether we have here in reality a new disease The clinical picture is certainly very distinctive the symptoms however are somewhat indefinite and the pathology quite obscure" In his second publication in 1904 (*16*) he reiterates the clinical manifestations of the conditions and adds additional cases

The first complete necropsy on a patient with the condition was published in 1904 by Weber and Watson (*18*)

Extensive reviews dealing with the disease have been written by Weber (*19 20*) Geisbock (*21*) Harrop (*22*) Zadek (*23*) Weber and Bode (*24*) and Harrop and Wintrobe (*1*)

An historical survey of the clinical picture of polycythemia rubra vera has been written by Dreyfus (*4*)

The use of the roentgen rays as a form of treatment in patients with polycythemia was first employed by Stengel in 1907 (*25*) This form of treatment had been mentioned by Vaquez in 1904 and also by Osler The irradiation of the entire body was suggested by Sgalitzer in 1935 (*26*) Turk introduced large doses of Fowler's solution in therapy of the disease The use of phenylhydrazine in treatment of this condition was first suggested by Morawitz and Pratt (*27*) and was actually employed for this purpose by Eppinger and Kloss in 1918 (*28*) Stone Harris and Bodansky advocated the use of acetyl phenylhydrazine in 1933 (*29*) In 1938 following extensive animal and clinical studies with radioactive phosphorus it was found possible by Lawrence and Scott (*30*) to administer non lethal doses of sodium radiophosphate to animals and cause inhibition of cell production in the bone marrow Subsequent studies showed that the material localized in bone bone marrow and rapidly growing tissues such as leukemic tissue (*31*) Based on these investigations radioactive phosphorus was administered to patients with polycythemia and leukemia in 1940 (*32*) and beneficial results were reported

Varieties of Polycythemia —There are several different varieties of polycythemia which should be carefully differentiated from each other A *relative polycythemia* is a condition in which through loss of blood plasma there is a resultant increase in concentration of the red blood cells the hemoglobin and hematocrit reading in the circulating blood There is no increase in the total blood volume in this condition

This may be present in patients with loss of water from the blood plasm due to persistent vomiting diarrhea excessive sweating curtailment of the fluid intake or in shock where an excessive quantity of the fluid of the blood passes through the capillary walls A relative polycythemia is transient and not associated with an increase in blood volume or the total blood mass as calculated from the blood volume multiplied by the hematocrit reading

An *absolute polycythemia is defined as an increase in the red blood* cells above normal which is associated with a greater red blood cell mass than normal The blood volume may not necessarily be increased This is because the blood mass may be larger than normal due to a greater concentration of the blood as indicated by a hematocrit reading which is above normal

Absolute polycythemia may be divided into two large groups namely, erythrocytosis by which is meant a polycythemia due to some known case such as congenital heart disease and erythremia which is a disorder of unknown etiology such as polycythemia rubra vera

Erythrocytosis or Secondary Polycythemia—In erythrocytosis the red blood cell count may reach high levels such as 8 0 to 10 0 million cells per cubic millimeter What evidence is available however, does *not* indicate that there is always an associated great increase in the blood volume such as that which is known to occur in erythremia (polycythemia vera) Furthermore in erythrocytosis there is usually slight if any associated rise in the white blood cell or platelet count and immature white blood cells are not present

In the Newborn—*It is known that at birth the values for the hemo* globin and packed red blood cells are usually high although the red blood cell count according to Wintrobe (33) is usually in the vicinity of 5 0 million per cubic millimeter with a variation of 1 0 million on either side of this average figure He finds however, that the average hemoglobin is 19 5 grams per 100 cc and the volume of packed red blood cells averages 54 cc This is therefore an absolute polycythemia but it persists for only a *short time Within two weeks a considerable change* toward normal occurs and in about three to five months all evidence of polycythemia has usually disappeared

In Cardiac and Pulmonary Diseases—The most striking evidence of erythrocytosis is observed in patients with congenital heart disease in which there is an intermingling of the arterial and venous blood such as occurs in the tetralogy of Fallot characterized by pulmonary stenosis a defective intraventricular septum right ventricular hypertrophy and dextral position of the aorta It is generally assumed that the stimulus to excessive blood formation in such conditions is the low oxygen tension although the exact process whereby this acts is unknown The red blood cell count is often from 7 5 to 8 5 million per cubic millimeter and

the hemoglobin varies from 18 to 24 grams. In a recent case of the tetralogy of Fallot which I observed the red blood cell count was 8.0 million per cubic millimeter, the hemoglobin 140 per cent, the total blood volume 8000 cc. and the hematocrit reading 80 per cent.

In pulmonary disease, especially emphysema, which may interfere with proper oxygenation of the blood, it is not uncommon to observe the red blood cell count and hemoglobin percentage to be above normal. Rarely do these rise to the levels seen in polycythemia vera or congenital heart disease. It is likewise true that polycythemia may occur in acquired heart disease, although this is not a very common finding and the changes are usually not pronounced.

Polycythemia at High Altitudes.—It has been known for many years that persons who reside at high altitudes for any length of time have red blood cell counts which commonly reach 7.5 to 8.0 millions per cubic millimeter. It is now thought that this increase in the erythrocyte count is attributable in large part to the stimulus of low oxygen tension to the formation of red blood cells and also to some extent to the contraction of the spleen and release of the cells into the circulating blood. Chronic mountain sickness, which is associated with this rise in the red blood cell count, has been recognized for many years. More recently it has been discussed by Monge (*34*). The effect of high altitudes on the red blood cell count of permanent residents in such areas is shown by the following figures: in Mina Aguilar, Argentina, an altitude of 4500 meters, the average red blood cell count for males is 6.46 millions per cubic millimeter; for male residents of Quilcha, Chili, altitude 5300 meters, the red blood cell count is 7.37 millions per cubic millimeter; in Morococha, Peru, altitude 4500 meters, the average male red blood cell count is 6.15 per cubic millimeter (*35*).

Association of Polycythemia with Intracranial Neoplasms.—An excellent review of neurogenic polycythemia was published by Drew and Grant in 1945 (*36*). The relation of cerebellar hemangioblastomas to polycythemia has been emphasized by Cramer and Kimsey (*37*) who studied a group of 53 cases with this type of cerebellar lesion. They found that in 18.0 per cent of the entire series of surgical cases of cerebellar hemangioblastomas and in 63.6 per cent of the group with multiple stage operations for recurrence of markedly vascular tumors there was a tendency toward polycythemia. This statement was based on an upper limit of normal of 5.0 million for women and 6.0 million red blood cells per cubic millimeter for men. In one male whose case history is given in detail the red blood cell count was 8.9 millions per cubic millimeter and the hemoglobin 15.0 grams per 100 cc. They regarded this patient as having Lindau's disease, namely, hemangioblastoma of the cerebellum with a (presumed hemangioblastomatous) cyst in the kidney complicated by polycythemia. They believe that the polycythemia is due to

hematopoietic activity of the hemangioblastomas but that this may represent merely a diathesis toward extramedullary hematopoiesis in the spleen and liver. Tissue cultures from the surgical specimen in one of their cases of recurrent vascular cerebellar hemangioblastomas provided evidence of erythropoiesis which they believe warrants further investigation.

A case of hemangioblastoma with polycythemia in which the red blood cell count reached a height of 7.82 millions per cubic millimeter with a hemoglobin of 21.9 grams and a white blood cell count of 6,850 per cubic millimeter is reported by Woolsey (*38*). Following the removal of a large hemangioblastoma there was a return to a normal red blood cell and hemoglobin level.

The co-existence of malignant tumors, especially hypernephroma, with polycythemia has been reported by Videbaek (*39*). In following 125 patients with polycythemia over a period of 20 years Videbaek found eight cases of cancer whereas the anticipated number based on a statistical study of the incidence of cancer in that part of the world should be three. Of the cases observed by Videbaek, however, two were hypernephroma with secondary polycythemia and one a metastasizing melanosarcoma with the same type of polycythemia. In his opinion idiopathic polycythemia does not appear to involve an increased risk of malignancy except leukemia. He emphasizes that the appearance of hematuria in a patient with polycythemia indicates pyelography since there may be a question of hypernephroma and secondary polycythemia.

Ayerza's Disease.—This disorder is characterized by a slowly developing bronchitis, dyspnea, cough, cyanosis and polycythemia associated with changes in the pulmonary artery and its branches. It was initially described by Abel Ayerza in 1901 in an unpublished clinical lecture at the National University of Buenos Aires (*40*). At this time he presented a patient with heart disease who had intense cyanosis ("cardiacos negros," black cardiacs) who showed hypertrophy and dilation of the right auricle and ventricle at necropsy and the microscopic evidences of chronic infection of the bronchi (*41*). A necropsy report of a similar case was published by Escudero in 1905 (*42*) and atherosclerosis of the pulmonary artery and its larger branches was found. The name "Ayerza's disease" was given to the condition by Marty in 1909 (*43*). Eleven cases were reported by Arrillaga, including Ayerza's original one, in 1912 (*44*). Two other publications by the same author appeared in 1913 (*45*) and in 1924 (*46*). An excellent summary of our present day knowledge is given by Leopold (*41*).

Patients with this disease usually give a history of a long-standing cough associated with chronic bronchitis. Gradually marked cyanosis and dyspnea appear which are often present when the patient is at complete rest. Usually there are no other signs of cardiac weakness such as

fullness of the veins of the neck an enlarged and tender liver, edema of the ankles or evidences of congestion at the bases of the lung Polycythemia is invariably associated Clubbing of the fingers may be present The pathologic findings according to Ayerza are chronic bronchopulmonary disease pulmonary emphysema striking right ventricular hypertrophy and pronounced changes in the pulmonary artery analogous to those observed in the vessels of the greater circulation in systemic hypertension In the opinion of Leopold (*41*) however in his recent review of the subject the disorder cannot result solely from pulmonary vascular changes which are invariably present in early adult life and become intensified with advancing years In his opinion the disease occurs most commonly in persons with syphilis and a chronic infection of the lower respiratory tract In discussing the etiology of the disorder Tidy (*47*) suggests that as seen in Brazil the syndrome may result from silicosis occurring at high altitudes and furthermore the possibility of a pulmonary bilharziasis as a main contributing factor should be kept in mind He believes that a more acceptable designation for the syndrome would be Ayerza s syndrome" I have had under my observation a man of 50 years who for two years had suffered from continuous dyspnea pronounced cyanosis and more recently developed edema His red blood cell count was 7 2 millions per cubic millimeter In all probability this patient had Ayerza s syndrome characterized by a slowly developing asthma bronchitis dyspnea cyanosis and polycythemia due to narrowing of the pulmonary artery or its branches as a result of syphilis or a congenital lesion

Polycythemia Due to Chemical Agents —The presence of abnormal blood pigments such as sulfmethemoglobin or methemoglobin in the circulating blood which may follow the excessive use of coal tar products occasionally causes a moderate polycythemia Such agents are thought to act as a stimulus to hemoglobin formation (*48*) Gum shellac according to Muller (*49*) is a powerful stimulus to the production of polycythemia normoblastosis and erythrocytic hyperplasia of the bone marrow Phosphorous poisoning which sometimes occurs in those engaged in the match industry may be associated with an abnormal increase in the red blood cells of the circulating blood In the opinion of Wintrobe (*50*) this results from the severe liver damage which the chemical causes It has been stated that polycythemia occurs in cases of poisoning by aniline and its derivatives such as nitrobenzol which is contained in some types of shoe dye and from toluyldiamine and atoxyl

Certain metals such as manganese mercury iron bismuth subnitrate and germanium have been said to produce polycythemia Of special interest is the relation of cobalt to this condition When this metal is administered to experimental animals either orally or subcutaneously an increase in the red blood cell count follows within a few days (*51 52 53*

54) *The effect of cobalt and other elements on the blood have been reviewed by Schultze prior to 1940 (55)* The action of cobalt in causing polycythemia in animals *is not known* It has not been observed in man Berk Burchenal and Castle (56) *report that when cobaltous chloride* was given orally in doses of 300 milligrams daily to patients with various forms of anemia there was some slight evidence of a beneficial effect It has been suggested that the element in some way interferes with the transport of oxygen by the erythroid cells of the bone marrow which leads to a cellular anoxia and consequently a compensatory polycythemia (57)

Polycythemia Following Massive Oral Vitamin B_{12} Therapy—Polycythemia resulting from the administration of massive doses of oral *vitamin B_{12}* derived from streptomyces is reported by *Barnard Kopet, and Stahl (58)* Two *patients one with probable Hodgkin's lymphoma and another with "subleukemic leukoblastosis* received daily oral doses as high as 1000 gammas of oral grade B_{12} for one month In one instance the red blood cell count reached a level of 6 7 millions per cubic millimeter with a hematocrit reading of 63 per cent and in the other it attained a level of 5 85 millions per cubic millimeter with a hematocrit of 55 per cent Previously the hemoglobin in the first case had been 10 2 grams per 100 cc and the patient was said to have had a normochromic anemia The other patient had a red blood cell count of 4 05 *millions per cubic millimeter before treatment* This subject needs further study and verification before one can accept the possibility that large doses of vitamin B_{12} when given to any patient with or without an anemia can produce a transient polycythemia Such a state has never been produced in my experience with the usual doses of liver extract or vitamin B 12 when given by any route in the usual therapeutic doses to any type of patient The possibility of producing excessively high red blood cell counts *in patients with pernicious anemia* by the usual doses of liver extract or *vitamin B_{12} given either orally or intramuscularly* is a hazard which does not exist

An interesting study of the effect of large doses of vitamin B_{12} has been made by Reisner and Weiner (59) who observed that most of the massive dose is excreted in the urine when it is given parenterally For example they gave as much as 1000 micrograms a week for periods of four six seven nine ten and 13 weeks but did not note any *greater improvement* in the anemia or *neurological manifestation* than would have followed the usual doses of the drug Furthermore patients with pernicious anemia in relapse who were given from 100 to 1000 micrograms by *injection* were found to excrete from 51 to 98 per cent of the injected dose in the urine in the succeeding seventy two hours They conclude that parenteral doses of more than 50 micrograms of vitamin B 12 are largely wasted and therefore have no advantage over *the smaller* doses in the treatment of pernicious anemia

ERYTHREMIA (POLYCYTHEMIA RUBRA VERA)

Synonyms.—Splenomegalic polycythemia; Vaquez's disease; Osler's disease; polycythemia with chronic cyanosis; myelopathic polycythemia (Weber); erythrocytosis megalosplenica (Senator).

Definition.—Erythremia is a chronic disease of unknown etiology, intermittently progressive in nature, characterized by an insidious onset, an absolute increase in the red blood cell count and the total red blood cell volume, and usually by evidence in the circulating blood of increased bone marrow activity. The clinical changes commonly observed are a peculiar reddish purple cyanosis of the skin and mucous membranes, moderate splenomegaly and various neurological and vascular manifestations.

Etiology.—*Age.*—This disorder almost always affects persons who are of middle age or older. It is stated by Weber (*20*) that the disease has its onset usually between the ages of 35 and 50 years, but that it has been observed in persons after 60 and in a number of instances before 30 years of age. Although cases have been reported as occurring in children, the diagnosis at that time of life, or in fact under 35 years of age, should be viewed with suspicion. In such instances great care should be employed to eliminate secondary polycythemia as the true basis for the abnormal findings. A case in a six year old boy is reported by Halbertsma (*60*) in whom many of the characteristics of the disease were present but, as the observer pointed out, leukocytosis and immature white and red blood cells, which are usually found in the blood in true polycythemia, were absent in this patient. In young patients the condition is rarely polycythemia vera but some form of secondary polycythemia associated with diseases of the heart or lungs.

Sex.—In the series of patients studied by Lucas (*61*) males were found to have the disease more commonly than females in a ratio of two or three to one. This was not true of Wintrobe's group (*62*) in which the females almost equaled the males in incidence. In Futcher's patients (*63*), however, there were 25 males and seven females.

Incidence.—Polycythemia is ordinarily regarded as a rare disease and this is undoubtedly the case, although it is probably not so uncommon as is generally supposed. It is reported by Futcher (*63*) that between the years 1899 and 1924, 32 cases of polycythemia vera were admitted to the Johns Hopkins Hospital, which gives an incidence of 0.06 of all admissions. Dameshek and Henstell (*64*) emphasize that the rarity of the disease may be more apparent than real. In support of their statement they report that in nine years at a relatively small hospital (200 beds) 20 cases were observed; in two years alone 11 new cases were seen. Since the diagnosis of polycythemia had not been suspected in several of these cases until after years of observation by many physicians, it is apparent that rarity of the condition, at least to some extent, results from a failure to recognize it.

Racial Distribution.—Although the disease may occur in any race, there is some evidence to indicate that it is rare in Negroes and relatively common in Jews. It is stated by Wintrobe (65) that of 32 cases of erythremia admitted to the Johns Hopkins Hospital only one was in a Negro although on the basis of the general admission ratio of Negroes to white patients one would have expected four or five.

The high incidence of erythremia in Jews was first emphasized by Turk in 1904 (66) and a renewed interest has been awakened in this subject by the studies of Reznikoff, Foot, and Bethea (67). They found that in their series of 134 patients 47.8 per cent were Jews of Eastern European origin whereas the same racial element accounted for only 9 per cent of the same general hospital population. Dameshek and Henstell (64) state that discussion with physicians at other hospitals in Boston has shown that cases of polycythemia are found among Jewish patients in many instances.

Familial Incidence.—The first article dealing with the congenital occurrence of polycythemia was that of Ambard and Fiessinger (68) although it is not clear that their patient had polycythemia early in life. In the following year, 1908, Nichamin (69) reported a case of polycythemia and for the first time recorded the familial incidence. Not only did the patient have polycythemia but also the mother and sister had splenomegaly and cyanosis. One of the most remarkable reports is that of Engelking (70) in which polycythemia was noted in the grandmother, the mother, and 5 children. A further study of this same family was made by Wieland (71) four years later. He concluded that the malady was constitutional and hereditary. In 1933 Spodaro and Forkner (72) summarized the previous publications dealing with the subject and came to the conclusion that there were only six instances of well established cases of familial polycythemia vera in the literature. These observers studied a family of 10 over a period of months and regarded seven of them as having familial polycythemia. They considered, however, that this condition differed from polycythemia vera as in the familial type which they observed the course was benign and there was no leukocytosis, eosinophilia, neutrophilia, elevated basal metabolic rate, or increased hemoglobin. They did not find that hemoglobin was abnormally increased in a single instance and the mean corpuscular volume was below normal in one half of the patients.

In 1939 Nadler and Cohn (73) reviewed the literature and reported on four cases in one family in whom the circulating blood volume was determined and the blood mass calculated for the first time in cases of this type. In the family observed by them there were 11 members out of a total number of 13 available for study. Of the 11 children four had definite evidence of polycythemia. The erythrocyte count varied from 7.48 to 8.50 millions per cubic millimeter and the hemoglobin estimations

from 21 0 to 24 3 grams per 100 cc of blood The hematocrit determinations were about 50 per cent above normal varying from 61 to 69 per cent In three of the cases the increase in circulating blood volume was double the normal value and occurred at the expense of the circulating plasma volume In one case the circulating cell volume was as great as the total circulating blood volume (three times as great as the normal circulating blood cell volume) of any of the patients examined The total circulating blood volume in this patient was 133 cc per kilo of body weight As the increased polymorphonuclear count the increased basal metabolic rate splenomegaly and symptoms referable to the disease are not a striking feature of familial polycythemia it has been assumed in the past by some who have studied the problem that the familial type of the disease is not the same as polycythemia vera These authors stress the point however that since Haden (74) finds an increased red blood cell mass to be characteristic of polycythemia vera it now seems justifiable to include "familial polycythemia in the former group of cases

An unusual association of two cases of polycythemia and one of myelogenous leukemia in a brother and two sisters is reported by Lawrence and Goetsch (75) All members of the family could not be studied but the mother also had a history compatible with the diagnosis of polycythemia This familial association is of interest on account of the relatively high incidence of leukemia occurring as a complication of polycythemia It is stated by the authors that there are eight authentic examples of familial polycythemia and 39 instances of familial leukemia reported in the literature They were able to discover only four instances of the occurrence of both leukemia and polycythemia in the members of one family

The Nature of Polycythemia —There has been a great deal of speculation concerning the mechanism of the production of the excessively high red blood cell count which is undoubtedly the main fundamental underlying disorder in this disease Theoretically it could be due to (1) an increased production (2) decreased destruction of red blood cells or possibly to (3) a combination of the two factors

It has been shown by Huff and his co workers (76) by means of radioactive iron studies that the rate of production of red blood cells in patients with polycythemia vera is greater than 0 8 per cent per day which is the rate if the cells survive for a normal life span of 120 days This would suggest that there is a decrease in the normal life span in this disease rather than an increased one which has been thought by some to account for the high erythrocyte count Using the labeled glycine technic London *et al* have found in a single case of polycythemia (77) that the life span of the red blood cells was normal The studies of Elwood and de Wardener (78) in which they transfused erythrocytes from patients with polycythemia vera into normal recipients and estimated the length of

survival by differential agglutination *showed that the life span of polycythemic cells was normal*

More recently studies bearing on this subject have been made by Berlin Lawrence, and Lee (79) in which the C 14 methyl labeled glycine technic was employed They concluded from their studies on patients with polycythemia that there are two classes of red blood cells in these patients, one with a short span and the other with a normal one It is their opinion that the rapid turnover of these short lived red blood cells is chiefly responsible for the greatly increased use of iron for the formation of hemoglobin in this disease Apparently some of the red blood cells in this disease do have a short span of life but the belief that long lived cells are responsible for the increased erythrocyte count is not tenable The rapid destruction however *is compatible with a greatly increased rate of* formation in the bone marrow a theory which meets with the most favor at present

The balance of evidence at present appears to indicate that the immediate cause of the elevation of the erythrocyte count is an abnormal increase in the activity of the bone marrow This view is supported by both positive and negative evidence There is uniform agreement that the red marrow constantly has the changes which are usually interpreted as indicative of increased activity namely the short bones of the body are filled with a red hyperplastic marrow in which there is an excess of normoblasts Furthermore there is no evidence indicating that the destruction of red blood cells is decreased below the normal rate There is no change in the fragility of the erythrocytes and at times there is an *increase* in the excretion of urobilin and stercobilin which would suggest that erythrocyte destruction is accelerated rather than decreased These facts then suggest definitely that the *main abnormality in the disease is an over production of red blood cells* but future studies may show that other subsidiary factors as yet unknown also play significant roles

If it is accepted that an excessive blood production is at fault in this *disease* then the question arises as to what may be the cause responsible for this Much speculation has arisen in regard to this problem and needless to say a definitive answer is not available This is mainly because we are ignorant of most of the fundamental facts regarding the normal control of both blood production and destruction Although many theories have been offered to explain these processes all are lacking in convincing proof The three theories dealing with the increased blood production in polycythemia which seem to be the most plausible are as follows (1) that some disturbance is present in the normal regulatory mechanism which controls the level of the red blood cells in the circulating blood (2) that the excessive red blood cell production may be attributed to anoxemia and (3) that the condition is analogous to a leukemia and therefore a process considered by many to be neoplastic in nature

It is attractive to consider that possibly a disturbance in the physiologic regulatory mechanism of erythropoiesis is at fault in this condition but there is little acceptable proof in support of this view There is substantial evidence largely arising from Castle's work on the etiology of pernicious anemia which indicates that at least one factor in the regulation of the maturation of the red blood cells is formed in the stomach by the interaction of the intrinsic factor of the gastric juice with some article of diet It is conceivable that an excess of the intrinsic factor might be present and create an increased stimulus to the formation of erythrocytes thereby producing a rise in the red blood cell count above normal This would imply however that there must also be a disturbance in the mechanism which normally prevents an increase in the number of red blood cells to abnormal heights All attempts to prove that the intrinsic factor is secreted in excessive amounts in polycythemia have not been convincing (*80 81 82 83*) Furthermore if one did concede that an abnormally large amount of intrinsic factor was capable of increasing the rate of red blood cell production there is no evidence which indicates that the mechanisms controlling the height to which the red blood count may rise are ineffective That there is such a mechanism is suggested by the knowledge that the administration of excessive amounts of liver or stomach material to patients with pernicious anemia is not associated with abnormally high red blood cell counts Nevertheless although proof is lacking it is possible that some disturbance of an unknown nature in the normal regulatory mechanism of the red blood cell count may play an important part in the etiology of polycythemia

A second view is that the increase in the red blood cell count may be associated with an anoxemia which serves as a stimulus to the overproduction of erythrocytes It is logical that such a theory should be developed because it has long been known that a polycythemia occurs in the blood of persons who reside for long intervals at high altitudes and also that a secondary polycythemia is present in patients with congenital heart disease in which there is an intermingling of venous and arterial blood It has been suggested by Harrop (*22*) that structural changes in the lungs which impede normal oxygen diffusion may be of importance in this connection Bence (*84*) offered the theory that it may be due to a lessened power of the red blood cells to absorb oxygen Another hypothesis by Saundby and Russell (*85*) postulated that in erythremia the capillaries are so dilated that the red blood cells are unable to unload their oxygen This they assume leads to a deficiency of oxygen in the tissues and a stimulus to the formation of red blood cells There is no substantial proof in favor of these theories at present It had been suggested some time ago (*86 87*) that the arteriolar and capillary lesions in the various parts of the body may give rise to anoxemia of the tissues and cause an over compensation of the bone marrow More recently Reznikoff Foot

and Bethea (67) have proposed the explanation that the vascular changes of the bone marrow especially in the capillaries may result in anoxemia of the marrow with compensatory or excess compensatory polycythemia In support of this view, they report that marrow specimens taken from patients with polycythemia showed capillary thickening probably fibrosis, and almost all of the samples which they examined there was in addition marked subintimal and adventitial fibrosis of the subarteriolar capillaries arterioles, and arteries Of the control specimens from patients with other disease, these changes were very rarely present It is reasonable to believe that such a change could explain the over stimulation of the bone marrow but the findings do not prove conclusively a causal relationship between the bone marrow findings and the increased level of the red blood cell count As Fitz and his associates say (88) one might postulate a vascular lesion with involvement of the bone marrow circulation which made the blood behave as though the patient to all intents and purposes were living at a high altitude"

Relationship between Erythremia and Leukemia —A third explanation of the overactivity of the bone marrow in this condition is that the fundamental alteration might be of a neoplastic nature, as many authorities consider leukemia to be and hence the marrow cells are assumed to have an unrestrained growth as is observed in a malignancy There is one *objection to this theory however as pointed out by Weber and that is* that the cells in polycythemia do not display an obvious invasive tendency *All evidence nevertheless indicates that there can be no escape* from the assumption of a close association between these two diseases *but as the etiology is unknown in both there is little more than can be said* about it The various aspects of the clinical picture which they have in *common lends support to the view that erythremia is perhaps a neoplastic* overgrowth of the erythroblastic tissues in the body in a way similar to that thought by many to occur in the leukoblastic tissues in leukemia

Evidence of the inter relationship between the two conditions is to be found in the following observations

1 In all cases of erythremia there is an increase in the polymorphonuclear neutrophils in the circulating blood and myelocytes and even myeloblasts may be present The white blood cells may increase to such an extent and the number of immature leukocytes be so large that the picture resembles myelogenous leukemia with the exception that the red blood cells and hemoglobin content of the circulating blood is increased

2 At necropsy in some patients with the clinical picture of erythremia there is extensive proliferation of the leukoblastic as well as the erythroblastic tissues The pathological findings may therefore resemble closely those observed in chronic myelogenous leukemia

3 In other cases after a *chronic course in which* the characteristic manifestations of erythremia have been present for a variable period of time an anemia has *been known to develop* with a persistent leukocytosis

and immature myeloid cells in the blood which simulates the hematological picture of leukemia very closely

4 In rare instances erythremia has been known to develop in patients with typical myelogenous leukemia (89)

5 Acute myeloblastic leukemia has been observed to develop in a case of polycythemia (*90, 91*) Recently (92) Hansen Pruss and Goodman have discussed this relationship and reported two cases of polycythemia in which leukemia developed just prior to death In both patients the leukocyte and differential counts remained normal until the terminal phase of the illness and in both the leukemic manifestations appeared while they were receiving roentgen therapy of the entire body for polycythemia. One patient died with acute leukemia of the Schilling type and the other of an acute myeloblastic leukemia

6 There have been a few instances reported in which cases of erythremia and leukemia existed in the same family (93 94)

7 The association of subleukemic leukemia with erythremia in a female age 52 years who developed gout during the course of her illness is discussed by Reifenstein (95) He emphasizes the close relationship between the two diseases

From the evidence cited above it must be admitted that the two diseases are closely allied conditions and as suggested by Minot and Buckman (96) the possibility that both may have a neoplastic etiology must be given serious consideration

It is my opinion that leukemia as a lethal complication occurs in about 2 to 4 per cent of all patients with polycythemia regardless of the type of previous therapy. Undoubtedly it also occurs in about the same per cent of untreated patients as a part of the spontaneous course of the disease The percentage of this transition is higher than given by others but such figures may be misleading as they are sometimes based on a comparatively small group of patients

It is reported by Dameshek (97) that one patient in 50 (2 per cent of the group observed by him) developed this complication without previous roentgen ray or radiophosphorus therapy This observer cites data from the Mayo Clinic to indicate that 1 per cent of patients with polycythemia who were not treated with any form of irradiation developed leukemia whereas 2.35 per cent who were treated with these agents developed the condition

Recently Stroebel Hall and Pease (98) have reported that in 148 patients with polycythemia who received radiophosphorus therapy four (2.7 per cent) developed acute leukemia and 1 (0 7 per cent) chronic myelogenous leukemia, making a total of 3 4 per cent This figure is not appreciably higher than the incidence of leukemia which occurs in patients with polycythemia who are not treated with irradiation of any type Further observations on a larger group of patients over a longer

period of time are desirable however before a definitive conclusion can be reached regarding this matter It is my own present opinion about which I feel reasonably secure that radioactive phosphorus and roentgen irradiation therapy is not responsible for the development of an increased incidence of leukemia in patients with polycythemia Furthermore if future studies should indicate that this conclusion is incorrect I am sure that the demonstrable risk incurred by such treatment will not be large In other words sufficient evidence is not at hand nor is it likely to be available which proves that irradiation of any form has an important hazard associated with it It should be kept in mind however that this form of treatment undoubtedly prolongs life and if it is granted that there can be a spontaneous conversion of polycythemia into leukemia then the longer survival period will be responsible inevitably for the occurrence of a larger number of such cases in which this transformation does occur This, obviously, is an indirect rather than a direct effect of the treatment

A remarkable case said to be *pernicious anemia, superseded by polycythemia vera* is reported by Galt Hunter and Hill (99) and reference is made to the scanty literature dealing with this association There does not appear to be any question concerning the diagnosis of polycythemia vera in the case reported as the patient had a red blood cell count which reached about 13 0 million per cubic millimeter with a hemoglobin of almost 20 grams per 100 cc of blood This was preceded by a severe macrocytic anemia with a red blood cell count of 2 5 millions per cubic millimeter and a hemoglobin of 8 8 grams per 100 cc a mean corpuscular volume of 113 cubic microns and a mean corpuscular hemoglobin concentration of 31 per cent There is however at least one *serious objection* to the diagnosis of pernicious anemia and that is the presence of a white blood cell count of 17 400 per cubic millimeter This rarely if ever occurs in such patients in relapse Furthermore although there is an achlorhydria this was determined following an Ewald meal rather than following the injection of histamine Although the bone marrow did show a slight increase in the number of megaloblasts it was not highly typical of pernicious anemia in relapse The possibility that the patient had pernicious anemia cannot be denied but in my opinion the patient more likely had some other type of macrocytic anemia Even if this is the case it was a remarkable association of two blood disorders which merited publication In my opinion this association was probably one of chance without reference to the administration of the large doses of vitamin B 12 or the liver extract

Pathology —There is extreme engorgement of all organs and distention of the veins with blood This sometimes causes varices which may occur in the esophagus intestine and elsewhere Often there are thromboses Hemorrhages either large or small are frequently found in the skin and mucous membranes and may be present in the brain meninges serous cavities and parenchyma of various organs

The spleen is enlarged and congested in most of the cases but occasionally it has been reported as normal in size. The splenomegaly is attributed to hyperplasia of the pulp and distention with blood. Microscopically in addition to hyperplasia of the pulp there is atrophy of the follicles. The red blood cells which are present in the spleen are almost all of the adult type only occasionally is a nucleated red blood cell seen. Hematopoietic foci which are likely to be of the leukoplastic type are occasionally present.

The liver is often enlarged due to the distention with blood. In some cases there may be associated cirrhosis or portal thrombosis. Myeloid metaplasia is occasionally present (*96*).

The bone marrow of the short bones is dark red in color and on microscopic examination is found to contain an excessive number of normoblasts as well as myeloblasts and promyelocytes. In other words there is *hyperplasia of all the marrow elements including the red blood cells white blood cells and megakarocytes*. Usually megaloblasts are not found. The marrow of the long bones are engorged chiefly with mature erythrocytes which is similar to the condition of the various organs of the body and thus is not interpreted as representing hyperplasia of the erythroblastic elements. Ordinarily the lymph glands show no changes but hematopoietic foci and deposits have been reported as present.

Symptoms and Signs—The Onset.—The appearance of the initial symptoms in this disease is so gradual that usually the patients have difficulty in stating just when the earliest manifestations of the condition appeared. This is undoubtedly because the increase in the number of red blood cells is gradual and furthermore it is apparently true that the erythrocyte count may be elevated for some time before symptoms become apparent. The initial complaints may be vague multiple and as neuropsychiatric symptoms commonly predominate patients are not infrequently regarded as suffering entirely from a psychoneurosis. In other instances it may be thought that they have a peripheral vascular disease hypertension heart disease or nephritis.

The earliest manifestations of the condition vary widely in nature. The initial complaint may be persistent headache dizziness ringing in the ears visual disturbances shortness of breath or asthenia. Rarely is the reddish discoloration of the skin the earliest evidence of the condition. Occasionally there are no complaints and the disorder is detected only as the result of a routine blood examination.

Changes in the Skin.—The alterations in the skin are among the most characteristic ones of the disease and often merely a glance at a patient will at once suggest the diagnosis. The color is a mixture of red and blue shades which give an appearance designated as a reddish blue cyanosis. In from 10 to 15 per cent of the patients however there are no changes in the skin whatsoever. For example in Christian's 10 patients (*100*)

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Cardiovascular Complications in Polycythemia Rubra Vera.—It is undoubtedly true that various pathological changes involving the vascular system are the most commonly encountered and therefore of greatest importance in this disease. The high incidence of thrombosis is easily understood as the circulation of the blood is sluggish, the rate being greatly retarded. It is easy to understand why this is true, as the vascular bed is greatly expanded, the blood volume is increased, there is a greater viscosity of the blood and the platelets are in larger numbers than normal. It has also been suggested by Oppenheimer (*103*) that the intima of the arteries is injured by a disturbed blood supply and from the wear and tear by fluid of increased viscosity, thereby contributing to arteriosclerotic changes. Thrombosis of an artery may occur in any part of the body and this may result in death. The process may involve the peripheral, cerebral, coronary, portal, hepatic, mesenteric, splenic and other blood vessels.

In the series of 100 patients studied by Brown and Giffin (*104*) it was stated that vascular disease occurred in 27 patients with polycythemia rubra vera. This did not include those with venous thromboses. A more recent study by Norman and Allen (*105*) shows that vascular complications of the disease were present in approximately one third of their group. The incidence of the various complications in their group of 98 *patients was as follows: intra-abdominal thromboses were proven in two* cases and possibly occurred in four more; coronary thrombosis, two cases; cerebral vascular disease, six cases; occlusive disease of the legs, seven cases of which three were regarded as arteriosclerotic obliterative disease and four were phlebitis; erythromelalgia, three cases; paraethesia, four cases; vasospastic disease (Raynaud's disease), one case.

Patients with polycythemia who have acute attacks of abdominal pain should be suspected of having thrombosis of an artery in the abdominal cavity. Changes of this nature involving one of the branches of the splenic vein are the commonest cause of pain in the upper left quadrant in these patients. Occasionally mesenteric thrombosis has led to an exploratory laparotomy. Thrombophlebitis of the gastro-epiglottic vein may simulate perforation of the stomach. Patients who develop thrombosis of the mesenteric or portal veins may have ascites with enlargement and cirrhosis of the liver.

Two types of sensory disturbances may occur in the extremities, especially the feet, in patients with polycythemia. One is acroparaethesia which consists of burning sensations without an increase in the surface temperature. There is a possibility that this sensation, as well as numbness and tingling of the extremities, may be associated with ischemia of nerve tissue as suggested by Fetterman and Spitler (*106*). In their opinion, involvement of the main arterial trunk to the nerve or simultaneous lesions in smaller branches or arterial twigs may be responsible for such

five gave no evidence of cyanosis or abnormal redness I have had under my observation two males about 50 years of age with undoubted polycythemia vera and elevated red blood cell counts in whom the skin and mucous membranes were normal in all respects The unusual appearance of the skin when present, involves the face especially the tip of the nose the cheeks and the ears Likewise the extremities are almost always involved Rarely does the characteristic shade extend down from the face further than the neck and hence it does not appear on the trunk As would be expected, it also involves the mucous membranes The buccal mucous membranes also those of the fauces, and pharynx and the tongue are frequently of a deep bluish color

The characteristic appearance is influenced to a certain extent by a cold or warm environment In cold it is intensified and with warmth the shade changes to one which has more of a reddish tint It can usually be demonstrated that placing the hands in warm water when they are blue and rubbing them can increase the circulatory rate and cause the color to change to red

Since the disease was first described it has been recognized that the color may vary from one patient to another and that it is not always the same in any given patient Osler s classic remark that a patient with this disease may be red as a rose in summer and indigo blue in winter fixes this characteristic in mind

The cause of the abnormal color in the skin and mucous membranes is the accumulation of reduced hemoglobin in the blood (*101*) which in turn is due to the engorgement of the capillaries and the reduced rate of flow through these small branches of the vascular tree

It is not uncommon to have purpuric spots appear on the skin of patients with this disease which may arise either spontaneously or from slight trauma Acne rosacea is perhaps the most common dermatological finding encountered in the disease A peculiar lesion described by Gans (*102*) is of importance because it resembles somewhat the cutaneous infiltrations which are observed in some patients with leukemia This condition was described as a group of rose colored firm irregularly rounded nodules which were very tender to the touch and were scattered over the trunk Histologically they were made up of a mass of minute vascular dilatations completely filled with erythrocytes and surrounded with masses of cells with small darkly stained nuclei and containing very little cytoplasm

Erythromelalgia is observed in some patients with the disease It is characterized by redness swelling and pain usually in the feet which is exaggerated by massage warmth a dependent position or exercise It is relieved partially or wholly by resting cooling and elevating the limb In most cases the condition is greatly benefited by therapeutic measures which reduce the blood count

was more than 150 millimeters of mercury and in 9 per cent it was more than 180 millimeters of mercury In two cases it exceeded 200 millimeters In 14 of the 163 cases there was mild congestive cardiac failure Coronary disease was present in 10 patients (6 per cent) four of whom had angina pectoris

Studies on circulatory adjustments in polycythemia rubra vera by Stewart Wheeler and Crane (*103*) have shown that at a time when the hemoglobin and the red blood cell count are increased above normal the arteriovenous oxygen difference is increased and the cardiac output per beat decreased The oxygen content of both the arterial and venous blood is greater than normal Left ventricular work cardiac size basal metabolic rate blood pressure and other functions of the circulation studied showed no consistent variation from normal in their patients When there was a reduction of the level of the hemoglobin and red blood cell count following therapy the arteriovenous oxygen difference decreased as did the output per beat and attained normal values when the hemoglobin and red blood cell count also reached normal values According to their findings there was a linear relationship between the quantity of hemoglobin and the number of red blood cells on one hand and the cardiac output on the other They interpreted these changes as possible compensatory mechanisms which spare the heart part of the burden of pumping an increased total volume of circulating blood which has an increased viscosity at normal velocity

Hemorrhages in Polycythemia —It appears paradoxical that an increased tendency to bleed may be present in a disease in which thrombosis also commonly occurs Nevertheless it is known that epistaxis is common and excessive hemorrhage may be associated with minor operations such as the extraction of teeth Bleeding from dilated esophageal veins has been reported According to Norman and Allen (*105*) the most important factor in the causation of hemorrhages is the great distention of the vascular bed Harrop believes (*22*) that there may be a variability in clotting and that at one time in a patient there may be an increased tendency to clot and at other times one to bleed excessively

Bleeding rarely occurs spontaneously but usually follows some type of trauma or surgical operation A profuse epistaxis may develop however without known cause and frequently excessive hemorrhage may follow the extraction of teeth tonsillectomy and other minor operations Certainly the diathesis should be taken into account when any type of operation is contemplated in a patient with this condition It has been recommended by Dameshek (*97*) that when such patients are operated upon particular attention should be paid to hemostasis and to the use of local hemostatic material He recommends blood or plasma transfusions with or without added fibrinogen before major operations In one of his patients in whom a hysterectomy was performed successfully 1000

ischemic changes This type of involvement is not benefited by the reduction of blood volume or by any form of therapy

The diagnosis of erythromelalgia is made possible in patients with polycythemia when there is a sensation of burning in the feet which is associated with an actual increase in the surface temperature of the skin Treatment in these cases is often of no avail indicating that the underlying pathologic process may be a disturbance of the nervous control of the circulation in the extremity

In some patients there are the classical symptoms of intermittent claudication such as cramps of the calf muscles either unilateral or bilateral following exercise with relief by a few minutes of rest With reduction of the red blood cell count and hemoglobin to normal there is usually relief from this symptom It is logical to assume that such a complaint arises as the result of two changes namely one a narrowing of the lumen of the vessels supplying the calf muscles due to arteriosclerotic changes and the other an increase of the blood viscosity which in itself would impair the circulation in the extremities

It has long been recognized that patients with polycythemia may have cerebral vascular lesions as the result of the tendency to either thrombosis or hemorrhage This has been emphasized by Christian *(100)* and others

Although patients with the disease may develop coronary thrombosis involvement of the coronary arteries does not appear to occur with the same frequency as thrombosis elsewhere in the body This may be because the stagnation of blood is less in the coronary vessels due to the constant active motion of the heart

It is considered by some *(107)* that hypertension is no greater in patients of different ages who have this disease than in normal persons and hence the association of hypertension and polycythemia is thought to be merely coincidental Gaisbock s syndrome *(21)* is a condition in which the patient has polycythemia and hypertension but no splenomegaly It is likely that such patients have true polycythemia with a coincidentally associated hypertension In some patients with this syndrome it has been observed that the spleen although not palpable when the patient was first seen subsequently became enlarged In a group of patients reported by Dameshek and Henstell *(64)* it was found that in approximately one half of them the systolic blood pressure exceeded 140 millimeters of mercury The blood pressure readings in these cases were as follows 170/100 230/140 170/80 170/110 200/100 200/100 150/90 148/100 165/110 In 7 of these cases or about one third of their group of patients with polycythemia there was an increase in the diastolic pressure to 100 millimeters of mercury or greater

In a review of 163 cases of polycythemia vera Tinney Hall and Giffin (108) found that in 65 (about 40 per cent) the systolic blood pressure

resulting from a cerebral thrombosis or hemorrhage but the underlying cause namely, the polycythemia is overlooked The paralysis may be transient and there may be a temporary aphasia It has been assumed that this is due to a pronounced slowing of the blood stream with a resultant anoxemia of the brain tissues Although this is a plausible theory it is one which is difficult to prove

Other neurological complications which had been observed are narcolepsy and catalepsy, loss of memory depression mental confusion and disorientation Clearly defined mental disease however is not commonly encountered in these patients

In a study of 163 patients Tinney Hall and Giffin (*110*) found that symptoms referable to the nervous system occurred in 78 per cent or 127 of the cases In 55 patients (34 per cent) neurological symptoms constituted the chief complaints The following table gives the incidence of the neurological manifestations in the 127 patients with the disease

MANIFESTATIONS OF POLYCYTHEMIA VERA REFERABLE TO THE CENTRAL NERVOUS SYSTEM

(127 Cases)

Symptoms	*Cases*	*Per Cent*
Headache	50	39.2
Vertigo	52	31 9
Weakness and fatigue	41	25 1
Nervousness	29	17 8
Visual disturbances	28	17 2
Severe neuroses with exhaustion	27	16 5
Paresthesias	23	14 1
Aphasia	13	8 0
Loss of consciousness	10	6 1
Tinnitus	8	4 9
Mental depression	7	4 3
COMPLICATIONS		
Cerebral thrombosis	27	16 5
Suspected brain tumor	8	4 9
Choked disk	4	2 4
Herpes	1	0 6
Combined sclerosis	1	0 6

Two cases of polycythemia in which the blood returned to normal following the removal of cerebellar hemangioblastomata are reported by Carpenter Schwartz and Walker (*111*) They review the relationship of the nervous system to polycythemia and suggest that in the cases observed the increased red blood cell count may have been of neurogenic origin See page 1033

Erythromelalgia which is associated with pain and congestion of the legs is considered in the section under the heading of peripheral vascular disease

cc of blood was first removed by venesection and a transfusion of fresh whole blood was given before and during the operation

The cause of the excessive bleeding in polycythemia is not known According to Norman and Allen (*105*), the most important factor is the great distension of the vascular bed It must be admitted that the cause of the bleeding is obscure as there is a high platelet count and no demonstrable defect in any of the known components of the normal clotting process Furthermore, there is no apparent abnormality of the capillaries It is of interest to note that such patients have a tendency to bleed not only when they are in relapse but also when the red blood cell mass is reduced in a remission

The Neurological Manifestations—Symptoms referable to the nervous system are among the most common encountered in this disease In many instances, however, they are multiple, vague and often misleading as they sometimes suggest that the patient is suffering from a psychoneurosis One of the most constant complaints is headache which varies in intensity from a slight fullness of the head to typical and severe migraine like attacks In many instances no relief is obtained from the administration of simple measures such as acetylsalicylic acid but often there is a rapid disappearance of this distressing symptom following venesection In some patients there is a history of typical migraine which has become intensified with the increase in the red blood cell count above normal

Other neurological complaints are dizziness nervousness insomnia attacks of faintness hot flashes and numbness and tingling of the hands and feet The latter symptom may be the outstanding complaint One of my patients who had been under treatment with radioactive phosphorous for several years insisted that he could foretell when the red blood cell count would be above normal because at these times there was always a reappearance of numbness of the hands and feet

Visual disturbances are common They consist of periods of dimness of vision and even transient blindness and specks bright spots and colored scotomata before the eyes Occasionally there is diplopia Embolism of the central artery of the retina has been reported Changes in the fundi are almost constantly present The retinal veins are engorged tortuous and deep blue in color which is in striking contrast to the red of the arteries Choking of the disks occurs occasionally Meniere's syndrome has been observed as a complication It has been attributed to distention and congestion of the vessels of the middle ear

As previously stated vascular lesions of the brain are not uncommon and are regarded as one of the most serious complications of the disease Such lesions which are more frequently due to hemorrhage than to thrombosis may result in hemiplegia aphasia or various other forms of paralysis which terminate fatally It is doubtless true that in some instances the cause of death is properly recorded as due to a hemiplegia

than in the control series direct information which has a bearing on the causal relationship between the two conditions is not available In some of their cases a history suggestive of active peptic ulcer antedated the onset of symptoms attributable to an increase in red blood cells Since the onset of polycythemia vera is so gradual however it is impossible in many instances to determine accurately the time relationships in the onset of the two diseases Boyd (*114*) considers that the polycythemia in these cases bears a causal relationship to duodenal ulceration He suggests that the tendency to thrombosis manifests itself in the first part of the duodenum producing a destructive lesion with necrosis

Bleeding often of considerable extent may occur in patients from rupture of esophageal varices thereby giving rise to hematemeses and tarry stools It is not uncommon to have loss of blood from hemorrhoids

Gout in Polycythemia —It has been said that the three most common types of blood diseases in which there is hyperuricemia and gout are leukemia familial hemolytic jaundice and pernicious anemia (*115*) In this connection it is of interest to note that Tinney Polley Hall and Giffin (*116*) report eight cases in a series of 168 patients with polycythemia who had gout as a complicating feature This gives a percentage of 4 7 They concluded that the hyperuricemia frequently associated with polycythemia vera is due to an increase in the catabolism of endogenous nucleoprotein which has its origin in the nuclear material liberated by an excess of maturing normoblasts It is also their belief that in patients who have gout the resultant additional increase in blood uric acid due to polycythemia vera may be sufficient to make a mild case of gout severe and a severe case of gout difficult to control

Splenomegaly and Hepatomegaly —Enlargement of the spleen occurs in about three fourths of the cases The edge is usually felt from one to four finger breadths below the left costal margin although in long standing cases it may extend to the umbilicus The size varies greatly and in individual patients there may be considerable fluctuation in the bulk of this organ without respect to treatment Either with or without treatment when the blood becomes normal the spleen may recede until it is no longer palpable The cause of the splenomegaly is generally considered to be engorgement with blood In general it can be said that the enlargement of the spleen follows the rise in the red blood cell count but in some instances it is claimed that the reverse has been true In some patients in whom the spleen is not palpable when first examined it later is found to be enlarged Pain which is attributed either to infarction with perisplenitis or to distention of the capsule may constitute one of the patient s chief complaints A friction rub over the splenic area occurs occasionally

In the study of their 163 cases Tinney and his associates (*117*) found that the spleen was easily palpable in 107 (66 per cent) It was enlarged

It is important to emphasize that 17 per cent of the patients seen by Tinney and his associates had severe neuroses and exhaustion. This when combined with their multiple complaints and especially when the purplish red color of polycythemia is absent not infrequently results in the erroneous diagnosis of a functional nervous disorder. In this connection it should be noted that seven of their patients (4 per cent) had symptoms of a psychiatric nature chiefly mental depression of varying degrees of severity.

Of especial interest was a group of eight patients in whom the localizing symptoms and signs were such as to suggest a brain tumor. In two of these cases a cerebral neoplasm was actually found. Choked disks occurred in four of their patients. The authors suggest when difficulty is encountered in the differential diagnosis between brain tumor and polycythemia vera it is advisable to treat the patient first for his polycythemia. With the reduction of the blood volume to normal there should be a definite improvement in the cerebral manifestations unless brain tissue has been injured by hemorrhage or thrombosis. If the cerebral manifestations persist despite treatment it would be evidence in favor of a brain tumor.

Gastro Intestinal Complications.—Engorgement of the abdominal vessels leading to congestion with symptoms referable to the liver, spleen, stomach, and intestine is not uncommon in patients with polycythemia. A sensation of fullness in the epigastrium with eructation of gas is one of the more frequently encountered complaints. Constipation has long been recognized as a symptom of the disease. Discomfort in the upper right quadrant of the abdomen due to congestion of the liver may occur. Pain in the upper left quadrant may be associated with thrombosis of a branch of the splenic artery or to an enlarged and congested spleen. Mesenteric thrombosis or thrombosis elsewhere in the body sometimes leads to symptoms which are erroneously regarded as an indication for surgical intervention.

There seems to be no doubt but what patients with this condition are prone to have peptic ulcers. Wilbur and Ochsner (*112*) found that they occurred in 8 per cent of the patients in their group of 134 patients whereas the incidence in patients with hypertension or in the population at large was only 2.0 and 3.2 per cent respectively. In the 20 patients observed by Dameshek and Henstell (*64*) four cases of peptic ulcer were found and it was suspected in another making the incidence in their small series either 20 or 25 per cent.

It was possible to demonstrate a peptic ulcer roentgenologically in 7 per cent of a series of 163 patients with polycytemia vera studied by Tinney, Hall and Giffin (*113*). In their opinion this represented an actual increased frequency in this disease. The authors believe that although the incidence of ulcer in polycythemia vera is significantly higher

of the patients with hepatic damage had gout. Ascites was present in six cases and pronounced jaundice in three before treatment with phenylhydrazine. A clinical diagnosis of portal thrombosis was made in six cases but this was confirmed by operation at necropsy in only two. The authors comment that hepatic function may be impaired in this disease for a number of reasons, namely: (1) distention of the portal circulation in the liver as a result of the increased blood volume, (2) stasis of blood flow due to the increased blood viscosity and sometimes by the development of congestive cardiac failure, (3) an increased load placed on hepatic function as a result of the excessive hemolysis associated with the action of phenylhydrazine, and (4) impairment of the nutrition of the hepatic cells due to blood stasis.

The Respiratory System.—Dyspnea is a common complaint and is undoubtedly related to an inefficient circulation and congestion of the lungs. Chronic bronchitis which is sometimes associated with a moderate amount of emphysema may be present. The lung markings in the roentgenograms may be conspicuous due to bronchial changes and to vascular congestion. Occasionally hemoptysis and hemothorax have occurred.

Pulmonary function studies have been carried out on five patients with polycythemia vera before and after phlebotomy by Newman, Feltman and Devlin (*119*). They found that in general the vital capacity is reduced, residual air is increased, total capacity is normal or decreased and the ratio of the residual air to total capacity is increased. The arterial oxygen saturation was normal or slightly reduced at rest and decreased with exercise. They believe that the increased blood viscosity and volume causes a decrease in elasticity and increase in the viscous resistance of the lungs. This in turn produces a decrease in the maximum breathing capacity and the vital capacity. With impairment in ventilation there is resultant arterial oxygen unsaturation and respiratory acidosis. With the possible development of severe degrees of anoxia along with other unknown factors there may be damage to the respiratory center and a vicious cycle may be established. They believe that in some cases of polycythemia there may be an increase in the red blood cell count and hemoglobin of the circulating blood to the polycythemic level as a result of primary respiratory center damage of undetermined etiology.

The Genito-Urinary System.—Bleeding from the bladder, vagina and uterus has been recorded. It is not uncommon to have a trace of albumin and casts in the urine but these findings are usually without great significance. Occasionally there is outspoken evidence of nephritis but it is not certain that this is in any way related to the polycythemia.

The Blood and Blood Forming Organs.—When the blood is shed it is thicker than normal and dark red in color. Its increased viscosity is

to the umbilicus in 17 and in 13 it was felt midway between the costal margin and the umbilicus In 21 it was merely mentioned as palpable It is of interest to note that in 17 (10 per cent) symptoms referable to this organ were present and in seven they constituted the chief complaints of the patient A clinical diagnosis of infarction of the spleen was made in 11 cases nine before treatment with phenylhydrazine and two following therapy In 15 of the cases in which the spleen was grossly enlarged, a leukemoid reaction was found and in five of these the changes were so striking that the blood findings closely simulated those of myelogenous leukemia Four of these five patients survived for long periods of time namely 12 15 20 and 23 years respectively after the diagnosis of polycythemia had been made

These authors believe that engorgement of the spleen with blood is an important factor in the splenomegaly as well as the hepatomegaly in this disease When the red blood cell count and the hematocrit reading are reduced the spleen may become smaller in size It was noted that in this series there seemed to be a definite correlation between the duration of the polycythemia the size of the spleen and the presence of a leukemoid reaction In those cases in which the duration of the polycythemia was greatest the largest spleens and the most pronounced leukemoid reactions were usually encountered

The liver is enlarged to about two finger breadths below the costal margin in approximately one half to two thirds of the patients, but occasionally there is gross hepatomegaly In two of the patients reported by Dameshek and Henstell (*64*) the edge was tender and extended to the umbilicus In both of these patients the chief complaint was pain in the right side of the abdomen which in one case was regarded as acute appendicitis and in the other as gallbladder disease

It was concluded by Sohval (*118*) in 1938 that hepatomegaly was present in two thirds of the cases of polycythemia and in 50 per cent of these the liver was either moderately or grossly enlarged According to this observer there was a definite relationship between the degree of hepatic enlargement and the duration of the polycythemia in his cases Furthermore he was of the opinion that there was more than a coincidental relationship between the two conditions He mentioned phenylhydrazine as a possible important cause in some cases

Some hepatic complication was found in 40 (25 per cent) of the 163 cases of polycythemia studied by Tinney Hall and Giffin (*117*) In 31 of the 40 cases the liver was palpable half way to the umbilicus The bromsulfalein test for liver function showed retention of the dye in nine cases In five cases a definite clinical diagnosis of cirrhosis of the liver was made In three of these severe and repeated hemorrhagic manifestations occurred usually in the form of purpura hematuria or hemorrhage after minor surgical procedures It is of interest to note that two

even return to normal. These spontaneous fluctuations should be taken into account when the various types of therapy prescribed for the disease are evaluated.

The red blood cells usually appear fairly normal in size and shape although one may find microcytes and occasionally macrocytes. As the color index falls during the later stage of the disease there is some hypochromia of the erythrocytes. It is not unusual to find nucleated red blood cells in the circulating blood and there may also be some evidence of polychromatophilia. The reticulocytes may be slightly increased, that is between 1 and 2 per cent.

The total white blood cell count is usually elevated to between 12,000 to 20 000 per cubic millimeter although counts of 25 000 are not uncommon and elevations as high as 50 000 per cubic millimeter have been recorded. The increased leukocyte count is characteristic and indicative of activity of the leukoblastic as well as the erythroblastic tissue of the bone marrow. Lucas (*61*) found in 96 cases that the white blood cell count was greater than 10 000 per cubic millimeter in 67 7 per cent of the cases. In Wintrobe's group of 22 cases (*122*) the leukocyte count varied from 12 850 to 58 000 in 12 patients and from 6300 to 11,550 in the remaining 10. It is important to note that there is an increase in the polymorphonuclear cells which usually average between 80 to 90 per cent and there is a "shift to the left" in the myeloid cells. Metamyelocytes are increased in number. There may be 1 to 2 per cent or more of myelocytes present but it is unusual to observe myeloblasts. There may be an absolute increase in the eosinophils, basophils and monocytes.

Characteristically there is an increase in the number of platelets of the circulating blood. In more than a majority of cases the total count is over 1 0 million and it may reach 3 0 million per cubic millimeter. The increase in the red blood cells, the polymorphonuclear leukocytes and the platelets indicate a general bone marrow activity which is typical of true polycythemia.

The bleeding time and coagulation time are normal although it is said (*123*) that the clot may not retract normally perhaps on account of the large red cell mass.

Bone Marrow.—The bone marrow when obtained by sternal aspiration is very cellular due to hyperplasia of the red, white and megakaryocytic elements. As all varieties of cells in the marrow are increased the proportion of the different types to one another is about normal. The nucleated red blood cells may be increased in numbers with the orthochromic normoblast predominating. Younger forms of the red blood cell series may be observed but megaloblasts are never present. The myelocytes and myeloblasts are often increased in number and in some instances there may be a great many megakaryocytes.

Blood Volume in Polycythemia.—The evidence has indicated in the past that in polycythemia vera there is an elevation in the total red blood

apparent when blood films are made or when it is drawn into the blood counting pipette It has been reported by Zadek *(23)* that the viscosity may be increased 5 to 8 times that of normal The specific gravity of the blood is likewise increased to between 1 075 and 1 080 as compared with a normal reading of 1 055 to 1 065 The changes in the specific gravity and the viscosity are directly due to the increased number of red blood cells as it has been found by Orlowski *(120)* that these values for the serum in patients with the disease are actually less than normal The sedimentation rate, as would be anticipated is greatly diminished

The red blood cell count is most frequently between 6 0 and 10 5 millions per cubic millimeter In untreated patients, the diagnosis is usually not considered unless the count is 6 millions per cubic millimeter or above Exceedingly high erythrocyte counts have been recorded but in some instances their accuracy is questionable According to Wintrobe *(121)*, when the red blood cells are normal in size (an average of 87 cubic microns) there is space for only 11 500 000 red blood cells per cubic millimeter of blood and it is not likely that life is compatible with blood which is made up entirely of cells without plasma Wintrobe further reports that the volume of packed red blood cells may be as high as 84 cc per 100 cc of blood in a case of congenital heart disease and 80 8 cc in a case of erythremia The highest hematocrit reading is recorded by Zadek (23) which is 92 cc in a patient with polycythemia vera with a red blood cell count of 10 370 000 per cubic millimeter

If the red blood cells are smaller than normal it is possible that more cells could be found per millimeter For example if the red blood cells have a volume of 61 cubic microns according to Wintrobe *(121)*, it would require 16 380 328 per cubic millimeter to fill the space entirely If the mean corpuscular volume was 52 cubic microns it would require 19 000 000

In polycythemia vera the red blood cells are usually normal in size that is the mean corpuscular volume varies between 86 and 96 cubic microns but it is not rare for them to be smaller than normal especially if phlebotomy has been performed as a therapeutic measure

The hemoglobin content of the circulating blood in this disease usually varies between 18 to 24 grams per 100 cc of blood which is from 115 to 154 per cent on the basis that 15 6 grams per 100 cc is equal to 100 per cent In the later stages of the disease the hemoglobin may not be proportionately increased in relation to the red blood cell count and this would cause the color index to fall to below 1 0 With this there is a reduction in the mean corpuscular hemoglobin and the mean corpuscular hemoglobin concentration

Both the red blood cell count and the hemoglobin percentage may vary considerably from day to day and there may be spontaneous remissions in which these values will be materially reduced or in some instances

As the hematocrit is invariably increased in this disease and the blood volume is likewise greater it must be true that the red blood cell mass which is obtained by multiplying the total blood volume by the hematocrit reading in percentage is likewise always increased and considered to be the most sensitive indicator of the changes in the blood In Hadens group of patients (*127*) the red blood cell mass varied from 2688 to 5551 cc in women which gave a value of 43 6 cc to 96 cc per kilogram This is to be compared to a normal value in women which he found to be 1482 cc for the total red blood cell mass with a value per kilogram of 26 4 cc In males the normal total blood cell mass he found to be 2326 cc which gave a figure of 30 cc per kilogram whereas in the male patients with polycythemia vera the total blood mass varied from 3223 cc to 8154 cc with a value per kilogram of 36 4 cc to 100 8 cc *It can be concluded therefore that in polycythemia vera the blood mass per kilogram may be three or even almost four times as great as it is in normal persons*

Other Laboratory Findings —Fragility of the Red Blood Cells —It has been reported by Minot and Buckman (96) that when the red blood cells from patients with polycythemia vera are placed in hypotonic salt solutions of descending strengths the initial hemolysis may be at a higher normal or lower level The minimum resistance may therefore in some cases be greater normal or less than normal The point at which complete hemolysis occurs however is often with the less concentrated solutions In some patients therefore there is a *lessened resistance* although the results are not always constant at different times It was suggested by Minot and Buckman (96) that the diminished resistance might be explained by the presence of older red blood cells in the blood of patients with erythremia which it is assumed have a lessened resistance to hypotonic salt solutions The greater resistance of some cells they suggest might be due to the presence of immature erythrocytes which are less fragile than normal Any deductions concerning these results must at present be considered purely tentative and subject to further investigations It does appear clear however that there is no definite evidence of a constantly increased or decreased resistance which is of such a degree as to play an important role in the etiology of the disease

In some instances there may be evidence of increased blood destruction as suggested by the level of bilirubin in the circulating blood which is above normal Furthermore there may be an increase in the urobilinogen and urobilin in the urine and stercobilin in the stools These findings are not however constant but at least they are evidence that there is no decrease in blood destruction which has been suggested as a possible cause of the increased red blood cell count

If it is concluded that there is an increased production of red blood cells which seems likely from the hyperplastic nature of the bone marrow

cell volume with little if any change in the plasma volume (*124, 125, 126, 127*). In secondary polycythemias, on the other hand, there was thought to be a total increase in the total red blood cell volumes but the plasma volumes were low (*128*). More recently Berlin *et al* (*128*) have determined the blood volume in patients with polycythemia vera and in the secondary forms of the disease by means of P 32 labeled red blood cells. They found that in 32 patients with polycythemia vera the red blood cell volume was elevated in 30 patients and the plasma volume was within normal limits in the entire group. Five patients with secondary polycythemia had elevated total red blood cell volumes but low plasma volumes.

They also observed that there was a fall in blood volume following treatment (usually with P 32) of patients with the disease. This diminution in some was associated with a fall in both total red blood cell volume and also in plasma volume; in others it could be accounted for by a fall in total red blood cell volume which was actually associated with a rise in plasma volume. The frequency of these two patterns was about equal. They were unable to observe any constant relationship between blood volume changes and a rise or fall in blood pressure, nor did splenic size appear to be a simple or direct function of blood volume. Finally, they concluded that it was not possible to estimate changes in blood volume from the red blood cell count or hematocrit in this disease.

It was determined by Haden (*127*) that the average blood volume of a group of 10 normal men whose average weight was 77 kg. (169.4 pounds) was 4960 cc., which gives a value of 64 cc. per kilogram of body weight. In 14 males with polycythemia vera who were observed by Haden, it was found that the total blood volume varied between 5965 cc. and 10,454 cc., and the blood volume per kilogram ranged between 75 cc. and 138 cc. In a group of 10 normal women with an average weight of 56 kg., it was observed that the total blood volume was 3702 cc. with an average of 64.4 cc. per kilogram. In six women with polycythemia vera he found that the total blood volume varied between 5443 cc. and 7659 cc., with a blood volume per kilogram of 74 cc. to 132 cc.

The Red Blood Cell Mass.—As the hematocrit readings are invariably higher than normal in untreated patients with polycythemia vera, it is obvious that the increase in the total blood volume is due almost entirely to the greater space occupied by the red blood cells in the circulating blood. Studies have shown, furthermore, that the plasma volume is but slightly altered if at all. According to Haden (*127*), the average normal hematocrit reading for females is 40 per cent and for males 45.5 per cent. Of the 20 patients with the disease, six females and 14 males, he found that the hematocrit readings were as follows: hematocrit 50 per cent or greater, 18 patients; 60 per cent or greater, 15 patients; 70 per cent or greater, seven patients. The highest reading of 78 per cent was recorded in a male.

Stewart and his associates suggest that these changes in the circulation may be compensatory in nature in an attempt to spare the heart part of the burden of pumping an increased total volume of circulating blood having an increased viscosity at a normal velocity

Blood Viscosity —According to the studies of Holbrook and Watson (136) using the Hess viscosimeter (137) there is no correlation between the blood viscosity and the color index but it has a direct relation to the number of erythrocytes They found that the normal viscosity was about 5 In a study of a group of patients with polycythemia vera Holbrook (138) reports that the viscosity values parallel those of the total red blood cell count Repeated determinations when plotted in the form of a curve did not show so many fluctuations which suggested that they were more reliable than the red blood cell counts He regards the viscosity tests as furnishing a reliable means for following the progress of patients under treatment In the patients reported by Holbrook the viscosity readings were as high as 9 or almost twice that of normal Wintrobe (123) cites Zadek (23) as stating that the viscosity of the blood may be five to eight times greater than normal

The specific gravity is increased as to be expected and is often found to be between 1 075 and 1 090 whereas the normal is given as 1 055 to 1 065

Diagnosis —The diagnosis of polycythemia vera should not be difficult provided the disease is kept in mind and if the blood is examined in patients who present the suggestive manifestations of the disease The disorder occurs most commonly in persons about 50 years of age and although it is observed in all races there is a higher incidence in Jews born in eastern Europe

A summary of the points in the history which are suggestive of the disease are given by Dameshek and Henstell (64) as follows 1 multiplicity of symptoms especially relating to the central nervous system 2 complaint of severe headaches including migraine 3 symptoms referable to vascular disease of the extremities 4 history of multiple thromboses venous and arterial especially of the extremities and 5 history of severe bleeding following even slight operative procedures Although none of these complaints are pathognomonic of the condition they call for an examination of the blood which may disclose the typical changes of the disease

The characteristic findings on physical examination are the reddish cyanosis which may not always be present the highly colored mucous membranes dilated retinal veins splenomegaly and hepatomegaly red hands and feet and sometimes hypertension

Information furnished by the laboratory examination is the most decisive sort and confirms or eliminates the diagnosis conclusively When polycythemia is present the red blood cell count is 6 0 millions

then at least at times, there also must be an increased *destruction* of red blood cells. Otherwise the red blood cell count would continue to rise. At a certain point, that is, when the erythrocyte count is increased but does not continue to rise further, there must be either a greater destruction of red blood cells or a temporary arrest in their increased rate of formation, or perhaps a combination of these two processes.

Gastric Analysis.—No characteristic changes occur in the gastric secretions. In some patients the hydrochloric acid is normal in amount, in others it is increased, and in still others there may be an achlorhydria. There is no evidence to indicate that patients with polycythemia vera have an increased secretion of the intrinsic factor of Castle although this has been suggested as playing a possible role in the etiology of the disease by Morris (*81*) and by Hitzenberger (*129*).

Urine Examination.—There are no characteristic changes in the urine although not infrequently albumin and casts are found.

Basal Metabolic Rate.—It is not uncommon to observe a moderately increased basal metabolic rate in some patients, although this is by no means a constant finding. Bliss (*130*) found a rate elevated above +10 in only 15 of his 23 cases. Values of +50 or higher have been noted occasionally. There is apparently some correlation between the level of the basal metabolic rate and the degree of activity of the bone marrow, but this is not constant. It has been suggested by Abbott (*131*) that the increase is due to the accelerated rate of formation of cells. Another explanation which has been offered by Isaacs (*132*) is that there may be a stimulating effect on the basal metabolic rate by the nuclear material which is liberated incident to the increased production of red blood cells. This was based on the observation that there is sometimes an increased amount of uric acid in the blood of patients with the disease.

Chemical Analysis of the Blood.—According to Wintrobe (*123*) a variety of chemical changes in the blood have been reported, but the results are so inconsistent that characteristic alterations cannot be said to occur. This observer has never found significant changes in the total serum proteins, albumin globin ratio, blood cholesterol, fats, non protein nitrogen constituents, serum calcium, magnesium, phosphorus, total serum base, or uric acid.

It is reported by Shelburne and Hanzal (*133*) that there is a persistently great increase in the endogenous uric acid excretion in polycythemia which they believe is associated with the accelerated formation of red blood cells. Gout has been reported occasionally as associated with the disease (*116*).

The Velocity of Blood Flow and Other Aspects of the Circulation.—It has been observed by Blumgart and his associates (*134*) that there is a definite retardation in the blood flow in patients with polycythemia vera which is in accord with the findings of Liljestrand and Stenstrom (*135*) and Stewart and his collaborators (*109*). As mentioned elsewhere

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per cubic millimeter or higher, and the hemoglobin is usually elevated over 120 per cent on the basis that 100 per cent is equal to 15.6 grams The *total blood volume is increased* as is the hematocrit reading which usually varies from 50 to 65 per cent Sternal bone marrow biopsy characteristically shows an intense hyperplasia involving all cellular elements There are signs of increased red blood cell formation such as the presence of nucleated red blood cells and cells showing polychromatophilia in the circulating blood

The condition must be differentiated from erythrocytosis or polycythemia secondary to a known cause such as congenital heart disease *emphysema Ayerza's disease (43) and that due to chemical or physical* agents Such cases ordinarily do not cause any diagnostic difficulty If an increased red blood cell count and hemoglobin percentage is found in the circulating blood of patients with chronic pulmonary disease or with cardiac lesions involving the right side of the heart either acquired or congenital it is at once apparent that the condition is one of secondary polycythemia In such conditions there is always arterial unsaturation which is never the case in polycythemia vera *Furthermore, in secondary polycythemia there is usually no elevation* of the leukocytes polymorphonuclear cells or platelets

The following points should be kept in mind in differentiating between polycythemia vera and secondary polycythemia associated with high altitudes and cardiac and pulmonary disorders *In polycythemia vera,* the bone marrow shows hyperplasia of all elements the erythrocytes leukocytes, and platelets are all increased in number in the peripheral blood the blood volume is very high the red blood cell volume is high the plasma volume is normal or increased and the arterial oxygen saturation is normal *In secondary polycythemia* the bone marrow shows excessive erythropoiesis only the erythrocytes only are increased in *the peripheral blood the blood volume is high the red blood cell mass* is high the plasma volume is low and the arterial oxygen saturation is diminished

Treatment —The chief basis for symptoms in patients with erythemia is the high red blood cell count which increases the viscosity of the blood and hence retards the rate of flow throughout the body As a result varying degrees of circulatory embarrassment are commonly observed The therapeutic indications therefore are clear namely to reduce the red blood cell count the hematocrit and the blood volume to normal limits Theoretically this should be accomplished more ideally by correcting the abnormally increased rate of production of the red blood cells which is the fundamental abnormality in the disease As the cause is unknown all therapeutic efforts must be directed necessarily toward known methods of decreasing blood formation increasing blood destruction *or removing blood from the body* The following methods of therapy have been employed

1 Increasing blood destruction by the use of phenylhydrazine lead acetate and other lead compounds
2 Decreasing blood formation by the administration of arsenic the roentgen rays radioactive phosphorus irradiation of the stomach or removal of the gastric secretions at frequent intervals
3 Removal of blood by venesection
4 A combination of venesection and irradiation therapy

Phenylhydrazine—This drug was introduced into the treatment of polycythemia by Eppinger and Kloss in 1918 (28) after its use had been suggested by Morawitz and Pratt (27) in 1908 Phenylhydrazine has been given the longest trial of any form of therapy in the disease and in general it may be said that the results are satisfactory although it should be administered with caution It acts by increasing the destruction of the red blood cells thereby causing a higher level of the bilirubin in the circulating blood Studies have shown that methemoglobin also may be produced Giffin and Conner (*139*) have pointed out the dangers of this form of therapy when given to elderly patients and to those with pronounced arteriosclerosis or evidence of advanced visceral injury The importance of minimum doses is stressed by these authors

Acetyl phenylhydrazine is probably the most effective form for clinical use It should be given with extreme care on account of the known cumulative effect which causes it to act for a week or ten days after the last dose has been taken The average daily initial dose by mouth is 0 1 gram in capsule for ten days followed by no medication for a week or 10 days If satisfactory changes have not occurred in the blood the course may be repeated In some instances an effect may be observed on the red blood cells after only two or three doses have been given It is usually possible to maintain the blood at a normal level by giving 0 1 gram every three to seven days One patient whom I have observed for three years has remained in good health and carried out a full day s work during this time by taking 0 1 gram every five to seven days He regulates his own dosage being guided by his own criterion of numbness and tingling in his feet *which he regards as a sign of inadequate therapy The presence* of a considerable number of immature red blood cells or a decided increase in the leukocytes is a danger sign and an indication to stop the treatment

Treatment with Irradiation—Irradiation has been used in the treatment of this disease for many years but until recently has not been looked upon with great favor At first the roentgen treatment was directed toward the spleen and various parts of the skeleton Irradiation with the roentgen rays is employed to some extent at present by applying doses systematically usually averaging 50 roentgens to the various bones of the body and the spleen It is sometimes used when there is splenomegaly and perisplenitis with associated pain but usually irradiation thus

per cubic millimeter or higher, and the hemoglobin is usually elevated over 120 per cent on the basis that 100 per cent is equal to 15 6 grams The total blood volume is increased as is the hematocrit reading which usually varies from 50 to 65 per cent Sternal bone marrow biopsy characteristically shows an intense hyperplasia involving all cellular elements There are signs of increased red blood cell formation such as the presence of nucleated red blood cells and cells showing polychromatophilia in the circulating blood

The condition must be differentiated from erythrocytosis or polycythemia secondary to a known cause such as congenital heart disease emphysema Ayerza s disease (*43*) and that due to chemical or physical agents Such cases ordinarily do not cause any diagnostic difficulty If an increased red blood cell count and hemoglobin percentage is found in the circulating blood of patients with chronic pulmonary disease or with cardiac lesions involving the right side of the heart either acquired or congenital it is at once apparent that the condition is one of secondary polycythemia In such conditions there is always arterial unsaturation which is never the case in polycythemia vera Furthermore in secondary polycythemia there is usually no elevation of the leukocytes polymorphonuclear cells or platelets

The following points should be kept in mind in differentiating between polycythemia vera and secondary polycythemia associated with high altitudes and cardiac and pulmonary disorders *In polycythemia vera* the bone marrow shows hyperplasia of all elements the erythrocytes leukocytes and platelets are all increased in number in the peripheral blood the blood volume is very high the red blood cell volume is high the plasma volume is normal or increased and the arterial oxygen saturation is normal *In secondary polycythemia* the bone marrow shows excessive erythropoiesis only the erythrocytes only are increased in the peripheral blood the blood volume is high the red blood cell mass is high the plasma volume is low and the arterial oxygen saturation is diminished

Treatment —The chief basis for symptoms in patients with erythemia is the high red blood cell count which increases the viscosity of the blood and hence retards the rate of flow throughout the body As a result varying degrees of circulatory embarrassment are commonly observed The therapeutic indications therefore are clear namely to reduce the red blood cell count the hematocrit and the blood volume to normal limits Theoretically this should be accomplished more ideally by correcting the abnormally increased rate of production of the red blood cells which is the fundamental abnormality in the disease As the cause is unknown all therapeutic efforts must be directed necessarily toward known methods of decreasing blood formation increasing blood destruction or removing blood from the body The following methods of therapy have been employed

1 Increasing blood destruction by the use of phenylhydrazine lead acetate and other lead compounds
2 Decreasing blood formation by the administration of arsenic the roentgen rays radioactive phosphorus irradiation of the stomach or removal of the gastric secretions at frequent intervals
3 Removal of blood by venesection
4 *A combination of venesection and irradiation therapy*

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employed does not decrease the size of the organ although the pain may be controlled

Spray irradiation total irradiation or treatment of the entire body by roentgen irradiation has been used in more recent years and is now regarded as effective and well tolerated This method of therapy was introduced in 1937 by Teschendorf (*140*) and first employed successfully in the treatment of polycythemia shortly after this time by Sgalitzer (*26*) who had treated 44 patients and reported good results in 42 In the intervening years this method of treatment has been given a fair trial and in general it may be said that the results have been favorably reported (*141 142 143*) The method employed by all of these observers is similar and is given by Pierson and Smith (*143*) as follows The patient is placed 2 to 2 5 meters from the anode of the therapy tube either in a chair or on a stretcher There is no lead protection of any kind and the patient faces the tube Thirty to 50 roentgens are given at a treatment which is administered every day or every other day This dosage is measured at the patient s distance and is also calculated from the intensity at 50 centimeters by the inverse square law In one instance 1 millimeter of aluminum only was used for filtration but otherwise 1 millimeter of aluminum and 0 5 millimeter of copper was employed The amount of filtration did not seem to make any difference in the results With 1 millimeter of aluminum and 0 5 millimeter of copper 52 r were delivered in 20 minutes at a distance of 215 cubic millimeters (200 kv peak valve tube half wave rectification Villard condenser circuit half value layer of 0 5 millimeter copper 1)

The total dosage used by Pierson and Smith varied from 728 in 17 days to 572 in 26 days and the amount given per dose was usually 52 roentgens although in one patient 34 roentgens were given It is their opinion that the leukocyte count level is the most accurate measure for determining the amount of treatment to give in any one case Daily leukocyte counts should be done and when the level of these cells drops below 4000 per cubic millimeter treatment should be stopped thereby avoiding an overdose Hemoglobin determinations and red blood cell counts are unnecessary during therapy because they cannot be expected to change as the result of the treatment until one to two months later

According to Sgalitzer (*26*) Hunter (*142*) and Gilbert (*144*) this method of treatment of total irradiation with the roentgen ray produces prolonged relief consistently in patients with polycythemia and is superior to other methods of therapy The length of the therapeutically induced remission varies in different patients In those treated by Pierson and Smith (*143*) there had been no recurrence at the time of publication of their article in 23 14 10 and seven months in their four patients Furthermore they state that if there is a recurrence of the manifestations of the disorder there is no reason why the roentgen therapy cannot be repeated

From these observations and those of others it seems likely that spray irradiation with the roentgen ray is a satisfactory method of therapy for patients with the disease. The evidence seems to indicate that it is effective. The possibility of over dosage must be kept in mind, but it apparently can be well controlled by observing the level of the white blood cell count. Another drawback is the latent period of one or two months before the results become apparent. In this interval, if the patient's symptoms warrant it, which they frequently do, almost immediate relief can be obtained by venesection.

Favorable results are reported by Reznikoff and Carty (*145*) in the use of general body irradiation (spray) in the treatment of 22 patients with polycythemia. They directed their treatment to the anterior and posterior torso alternately with 25 to 50 roentgens every other day or daily, depending upon the tolerance of the individual patient. A total dosage which varied between 100 and 550 roentgens was given. Of the 22 patients, 21.4 per cent had remissions which continued for more than six months; in 11 patients the remissions were continuing when the article was submitted for publication; four failed to have remissions; in two the therapy was interrupted; in one the treatment was given too recently for evaluation; two patients did not return for a follow up examination. These observers define a remission as the return and maintenance of the red blood cell count to a level of less than 6 million. Of the remissions, 11 lasted more than one year, two which are continuing for more than two and one half years. They did not think that the present evidence indicated that radio phosphorus had any advantage over roentgen spray irradiation in this condition. It is the opinion of Richardson and Robbins (*146*) that spray irradiation is a sound method of treatment as it aims to inhibit an overproductive bone marrow. After a long follow up of their patients, they conclude that patients thus treated may remain well for years, that a hypochromic anemia is not produced as it may be with repeated phlebotomies, and that it does not cause a conversion of polycythemia to leukemia. The disadvantages they list are the production of roentgen sickness, the time and effort in completing the course of treatment, the possibility of producing a refractory anemia or of other long range deleterious effects. In their opinion, however, spray irradiation is the treatment of choice.

Treatment of Polycythemia with Radiophosphorus.—The introduction of radiophosphorus (P 32) with a half life of 14.3 days as a form of treatment for this disorder has been a distinct therapeutic advance. Following extensive animal and clinical studies with the substance, Lawrence and Scott (*147*) found that non lethal doses of sodium radiophosphorus could cause inhibition of cell production in the bone marrow of animals. It was observed later by Lawrence and his associates (*31*) that the material localized in the bone marrow and rapidly growing tissues of

animals which is a situation similar to that present in leukemia These studies led to the clinical use of this agent as a form of treatment in leukemia and polycythemia (*147*)

Since then many studies have proved its great usefulness in the treatment of both of these diseases In an article published in 1949 (*148*) Lawrance summarizes his experience in treating 121 patients with polycythemia with isotope P 32 He emphasized that many observers have reported on the satisfactory use of this therapeutic agent in this condition His own *observations show that patients thus treated have an average* age at death of 67 years after an onset which has occurred at the average age of 50 7 years In his opinion, patients with polycythemia who have received this form of treatment have the same favorable outlook as those with diabetes mellitus treated with insulin and those with pernicious anemia when treated with liver

Likewise Stroebel Hall and Pease (98) conclude that radiophosphorus treatment is successful in producing remissions of more than one year s duration in 90 per cent of the cases of uncomplicated polycythemia In 50 4 per cent of the cases, the remission persisted for one to two years in 31 6 per cent it lasted two to four years and in 4 5 per cent it had a duration of more than four years

The use of radiophosphorus in the treatment of polycythemia is considered to be the optimum form of therapy by Wiseman and his associates (*149*) after an extensive experience with all types of therapeutic agents They consider that the objective of treatment is the control of excessive hyperplasia of all the *marrow elements* with the *minimal discomfort* and danger to the patient They believe that the use of radiophosphorus fulfills all of the hematological and clinical requirements of a therapeutic agent in this disease completely and safely The oral method of administration in their opinion is as satisfactory as the parenteral method of administration although a large majority of patients are treated by intravenous injection Their method assumes that in a fasting patient without diarrhea 75 per cent of the administered dose will be absorbed They multiply the (absorbed) dose desired in a given patient by four thirds giving the larger amount thus taking into account that approximately 25 per cent *will not be absorbed*

In the group of 121 patients treated by Lawrence (*148*) there have been 21 deaths The causes of death have been generalized arterio*sclerosis* five leukemia five neoplastic disease three coronary occlusion three cardiac failure two portal thrombosis one anemia and leukopenia one cerebral thrombosis one With the possible exception of leukemia the main causes of death in this group are the ones which occur commonly in persons of this age group

According to Jacobson and Smith (*150*) if the incidence of leukemia and especially acute leukemia is not increased by the use of radio

phosphorus it is or will be the treatment of choice. These observers believe that it is superior in its therapeutic effect to spray irradiation because in general the remissions produced by P 32 appear to be longer and more complete than those produced by any form of treatment. According to Erf and Lawrence (*151*) the first evidence of significant decreases in the hemoglobin levels occurs in approximately 100 days after an effective dose of radiophosphorus has been given. This material has the advantage furthermore of never producing nausea or vomiting or any other ill effects when administered in therapeutic doses. It is possible that in the future other radioactive agents will be found to be superior. Our experience with radioactive phosphorus in the treatment of this disease at the Simpson Memorial Institute has been most satisfactory. When the material becomes available for more widespread use it is likely that it will be the method of choice in the treatment of this disease.

Radioactive phosphorus is administered in a solution of sodium or potassium phosphate. It may be given by either the oral or intravenous route. After oral administration approximately 25 per cent is unabsorbed from the gastro-intestinal tract. For this reason the intravenous method is generally preferred. The solution containing the calculated dose of radioactive phosphorus is sterilized in a boiling water bath for 30 minutes and then diluted with about four times its volume of physiologic salt solution and administered by gravity. Since the amount of radioactive phosphorus required to produce the desired therapeutic effect varies greatly in different patients it is safest to commence with a small dose of 3 to 5 millicuries and wait two months before considering the need for further therapy. At the end of that interval a subsequent dose should not exceed 3 millicuries. Decreases in the leukocyte and platelet levels precede by several weeks any appreciable change in the erythrocyte count following administration of radioactive phosphorus. The leukocyte level is therefore a valuable guide in the use of this form of treatment.

A word of caution should be said concerning the importance of a thrombocytopenia prior to treatment of patients with radiophosphorus. A patient with this disorder at the Simpson Memorial Institute had a red blood cell count of 8.9 millions per cubic millimeter, a hemoglobin of 17.5 grams per 100 cc. of blood, a hematocrit reading of 66 per cent and a platelet count of 115,000 per cubic millimeter. The cause for the low platelet count was not known for certain but it may have been due to an x-ray treatment given about four months before. The patient was given 8.4 millicuries of P 32 intravenously. About five weeks later the patient developed extensive purpuric lesions and the platelet count was found to be below 5000 per cubic millimeter. The red blood cell count and the hemoglobin were within normal limits but at one time following therapy the white blood cell count had decreased to 2450 per cubic

animals which is a situation similar to that present in leukemia. These studies led to the clinical use of this agent as a form of treatment in leukemia and polycythemia (*147*).

Since then many studies have proved its great usefulness in the treatment of both of these diseases. In an article published in 1949 (*148*), Lawrance summarizes his experience in treating 121 patients with polycythemia with isotope P 32. He emphasized that many observers have reported on the satisfactory use of this therapeutic agent in this condition. His own observations show that patients thus treated have an average age at death of 67 years after an onset which has occurred at the average age of 50.7 years. In his opinion, patients with polycythemia who have received this form of treatment have the same favorable outlook as those with diabetes mellitus treated with insulin and those with pernicious anemia when treated with liver.

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In the group of 121 patients treated by Lawrence (*148*) there have been 21 deaths. The causes of death have been: generalized arteriosclerosis, five; leukemia, five; neoplastic disease, three; coronary occlusion, three; cardiac failure, two; portal thrombosis, one; anemia and leukopenia, one; cerebral thrombosis, one. With the possible exception of leukemia, the main causes of death in this group are the ones which occur commonly in persons of this age group.

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the advantage of being easily available to all practitioners and its effects can be very accurately controlled Furthermore its use is not associated with any untoward effects as may be the case when the roentgen ray and phenylhydrazine therapy are employed

The two possible disadvantages are first the possible stimulation of red blood cell formation by the therapeutic removal of blood and second the greater reduction in the hemoglobin than in the red blood cell count The possibility that venesection may stimulate the bone marrow to a greater production of red blood cells is based on the observation that there is increased bone marrow activity in humans and experimental animals following hemorrhage It should be pointed out however that such conclusions are based on studies in which a sufficient amount of blood is removed to cause a definite anemia Most certainly stimulation of the marrow would be expected under those conditions The situation is different however in patients with polycythemia Here only a sufficient quantity of blood is removed to bring the level of the hematocrit and hemoglobin to normal and *never should an anemia be produced* There is no evidence that an important stimulation of the bone marrow results under these circumstances (*151 155 156*) Corroborative evidence in support of this is found in the observation that there is no reticulocyte increase in the circulating blood following the removal of 500 cc of blood from a normal individual

More recently Hines and Darnall (*157*) have expressed the belief that the removal of as much as 1500 cc in a 14 day period does produce evidence of erythropoietic stimulation as evidenced by a slight rise in reticulocytes and changes in the bone marrow cytology As a result they suggest that smaller amounts namely 200 cc to 250 cc be removed at two-week intervals as by so doing the stimulating effects can be circumvented On the other hand Stephens and Kaltreider (*156*) do not believe that larger venesections are responsible for a significant stimulation of the marrow for these produced a reticulocytosis only occasionally Furthermore in these instances they attributed such a rise to the fact that the tissue stores of iron were increased presumably as a result of previous blood destruction from the administration of phenylhydrazine It is logical to assume that the removal of a large quantity of blood from these patients results in the loss from the body of considerable amounts of iron and other blood building materials This in itself may have an inhibitory effect on the regeneration of erythrocytes

Another possible disadvantage is that when the hemoglobin and hematocrit readings are reduced to a normal level the red blood cells may still be in the vicinity of 6 0 per cubic millimeter or more In other words a microcytosis and hypochromia may be produced This is not necessarily disadvantageous since the increased blood volume and viscosity of the blood which are responsible for the stasis and retardation of blood flow are associated with an increase in the hematocrit reading

millimeter. *Sternal aspiration showed a normal number of megokaryocytes* but they were distinctly abnormal and some could be recognized as megokaryocytes only because transition forms were observed between these bizarre forms and normal cells. The case is reported in detail by Andrews (*152*) who warns that radioactive phosphorus should be used with caution especially in patients who already have thrombocytopenia.

The Use of Potassium Arsenite.—The use of arsenic in the form of a *solution of potassium arsenite U S P (Fowler's solution) as a safe and* reliable method of treating polycythemia has been advocated by Forkner, Scott and Wu in 1933 (*153*). Turk in 1904 (*66*) had reported that the drug produced satisfactory results in one patient. Sufficient evidence bearing on its effectiveness had not been accumulated until the studies of Forkner and his associates proved conclusively that it is of value in the treatment of this disease. They treated six patients and in each case *there was improvement in the hematological manifestations and in five* cases the hemoglobin and red blood cell count returned to normal. The dosage recommended was as follows: beginning doses of 3 to 4 minims (0.18 to 0.24 cc.) are given three times daily. The initial dose is continued for two days and then the total daily dose is increased by 3 minims. This amount is given for two days. Thereafter the dose is increased at the same rate until the first sign of intoxication, anorexia, is noted. This usually occurs when the total dose reaches about 24 minims (1.48 cc.) daily. When the amount administered reaches 8 to 10 minims three times daily the further increments in dosage must be added at a rate not greater than 1 minim to the total daily dosage. In general the best results are attained when the dosage is increased to a point where either the desired effects are produced or until the limit of tolerance is reached. When either one of these objectives is attained the dose should be decreased or omitted for several days and then resumed in amounts of about 5 minims three times daily. *The medication, well diluted in orange or tomato juice, is best given with or immediately following meals.*

From a theoretical standpoint this drug is a logical one to give because it acts largely by depressing the rate of formation of the red blood cells which is abnormally increased in the disease. In large doses it also has some effect on increasing the rate of destruction of the red blood cells. This preparation has one serious objection in my experience which prevents me from using it in patients with the disorder, namely, the loss of appetite, nausea and vomiting which so commonly occurs frequently results in an important loss of weight and this with the disagreeable gastro-intestinal symptoms usually causes the patient to turn against the drug. In the treatment of this disease I would rate the solution of potassium arsenite below venesection, irradiation and phenylhydrazine.

Treatment by Venesection.—The treatment of this disease by venesection alone is a simple and fairly satisfactory method of therapy. It has

In recent years there has been a tendency to combine venesection and roentgen ray therapy in an attempt to make the blood become more nearly normal The removal of blood affects the level of the hemoglobin primarily and the roentgen ray therapy deters the rate of regeneration of the red blood cells From a theoretical standpoint this combination has much to recommend it but further observations are necessary to evaluate its effectiveness In such patients after venesection and reduction of the blood to a normal hematocrit reading my patients have received a total dosage of about 100 r in the form of "spray" roentgen therapy over the course of several days

The Use of Nitrogen Mustard Therapy in Polycythemia Vera —This agent was introduced in the treatment of polycythemia because it was known to have a suppressive action upon hematopoietic tissue Its use was reported in a preliminary note by Jacobson and his associates in 1948 (*159 160*) Following these studies others have been made concerning its efficacy in the treatment of this disorder (*161 162*) When the standard dose of methyl bis (B chloroethyl) amine hydrochloride of 0 1 per kilogram is given over 4 consecutive days with a total four day dose which does not exceed 24 milligrams there is usually a prompt suppression of erythropoiesis This is shown by the decrease in the reticulocytosis and a decline in the levels of the hemoglobin the red blood cell count and hematocrit readings which reach their lowest level in four to five weeks following the treatment In the group of patients studied by Jacobson and his associates phlebotomies usually preceded the nitrogen mustard therapy in order to reduce the hematocrit to 60 per cent This was done to lessen the hazard of thrombosis during the early phase of treatment Nitrogen mustard was then administered in the standard doses with an average reduction in the hematocrit from 59 to 44 per cent in 4 4 weeks The average period of remission was 6 5 months It is the conclusion of these authors that the prompt hematologic and clinical response to this therapeutic agent is considered to be advantageous and warrants additional study and evaluation The possible disadvantages are the nausea and vomiting which commonly follow the injection of the drug and persist for two to four hours Also as emphasized by Jacobson and his associates (*163*) the possibility of aggravating the inherent tendency of polycythemia toward leukemia must be considered While undoubtedly nitrogen mustard does suppress the bone marrow activity and produces beneficial effects in patients with polycythemia it is less effective than treatment with roentgen irradiation or radioactive phosphorus Hence it cannot be recommended at present as a treatment for routine clinical use

Miscellaneous Forms of Treatment —Recently Falconer (*164*) has reported satisfactory improvement in patients with polycythemia following the intravenous use of colloidal lead phosphate in doses of 10 cc

This determination depends on the number and on the size of the cells Theoretically therefore, it should not make a significant difference if the hematocrit is reduced either as the result of a decrease in the size or number of red blood cells

According to Haden (*158*), it is imperative to withdraw a sufficient quantity of blood and he advises that the excess of erythrocytes be removed in a relatively brief interval if no contraindications arise He gives an illustrative example as follows

Male patient, weight 70 kilograms

The hematocrit reading was 60 cc of cells per 100 cc of blood and the total blood volume was 8000 cc

Red cell mass 8000 × 60 = 4800 cc

Normal for patient 70 kg (body weight) × 30 cc per kg (normal blood mass) = 2000 cc

Excess cells 2800 cc

As blood is withdrawn the hematocrit reading will of course fall finally reaching a normal value of 46 cc He calculates the mean hematocrit reading as 52 cc ; therefore to be removed, can be calculated as follows (2 700/52) × 100 = 5200 cc According to this observer it may not be possible to reduce the blood to normal during the first course of treatment although he has removed as much as 7000 cc of blood in one week in a patient with a cell mass of 9096 cc when the normal for his weight was 2100 cc

A safe procedure from a practical standpoint is to remove 300 to 500 cc of blood every third day and determine the hemoglobin concentration, the red blood cell count and the hematocrit reading before each venesection . The venesections should be continued unless some contraindication develops, until the hematocrit readings reach about 48 to 50 per cent Then the venesections should be stopped . It does not seem wise from my experience to remove more than 1500 cc during the course of any one series of treatments If the blood is not within normal limits at that time no further venesections should be done for four to six weeks when they can be resumed if the indications are still present

While it is more accurate from a theoretical standpoint to calculate the blood mass and be guided accordingly the estimation of the blood volume which is necessary for this determination presents some technical difficulties and is not ordinarily done It is thought however that the red blood cell count the hematocrit determination and the hemoglobin estimation probably serve as adequate criteria for the determination of the amount of blood to be removed In general it should be kept in mind that the hemoglobin often falls to a level of slightly below normal when the hematocrit reaches a normal level and often at this time the red blood cell count is still elevated above 6 0 million per cubic millimeter

complaints) and there is difficulty and uncertainty in controlling the level of the cells. *Roentgen irradiation* may be followed by unpleasant roentgen ray sickness; considerable time and effort are required, and it may be expensive. It is the opinion of Wiseman and his associates, with which I concur, *that radioactive phosphorus possesses distinct advantages over all other methods of treatment*. If available, I believe that it is the treatment of choice. Total body roentgen ray therapy is second and repeated phlebotomy with or without limitation of iron intake is third.

In the presence of symptoms patients should be treated immediately by phlebotomy with the removal of 500 cc. of blood. This procedure should be performed every other day until the hematocrit reading is approximately 50 to 55 per cent. In the case of elderly or debilitated patients, 300 to 500 cc. should be removed only once or twice weekly.

Radiophosphorus (P-32), if available, is the treatment of choice. It should be given in an initial dose of 3 to 5 millicuries intravenously and the blood examined at intervals of six to eight weeks thereafter. If at this interval the values are still elevated, then about 3.0 millicuries should be given intravenously. This dose may be repeated every eight weeks until normal levels of the hematocrit, the hemoglobin and the red blood cell count are attained. No further medication is given as long as the blood remains within normal limits.

If radiophosphorus is not available, then the next best treatment in my opinion is total body irradiation (see page 1063). The blood should be examined at intervals of six to eight weeks also as a guide for further therapy.

If it is not feasible to give either radioactive phosphorus or roentgen irradiation, then the patient should be treated with phlebotomy until the hematocrit is reduced to about 50 to 55 per cent and the other blood values are approximately normal. The patient should be placed on an iron poor diet from the beginning of this treatment. This diet consists in the curtailment of foods rich in iron such as red meat, liver and eggs, various green vegetables as spinach, string beans and Swiss chard, certain cereals especially hominy, oatmeal, whole wheat and bran, and sea food such as shellfish including oysters, clams and lobsters. Fish is advised three times weekly, chicken or other poultry twice weekly and lamb or veal once or twice weekly. Red meat is given only once weekly. It is recommended that two to four glasses of milk be taken daily.

Prognosis and Course.—Polycythemia vera must be regarded as a chronic disease but one which over the course of 10 to 20 years or longer is slowly progressive and eventually fatal. In some patients the disease may be asymptomatic for some time as was the case of two patients observed by Rosenthal and Bassen (*170*). In one of their patients with a red blood cell count of 10,670,000 per cubic millimeter and a

in which each cc contains 3 7 to 3 8 milligrams of metallic lead He treated 11 patients with lead compounds orally and intravenously over periods of time varying approximately from one to five years Nine of these patients were relatively free of symptoms during treatment and were able to continue work He concludes that in selected cases of polycythemia vera colloidal lead phosphate is efficient in controlling the symptoms and in reducing the blood level It should be emphasized that the *dangers of this form of treatment are real* and the results are certainly no more satisfactory or as good as those following other forms of therapy While the effect of the administration of lead is of interest this method of treatment cannot be recommended

Various attempts to decrease the amounts of the erythrocyte maturing factor by diminishing the secretion of the intrinsic factor of Castle have been made and are of interest from a theoretical standpoint Singer (*165*) performed a gastrectomy in a patient with polycythemia and a duodenal ulcer It was reported that the patient s erythrocyte count was 4 6 million a year later In 1934 Hitzenberger (*129*) made an attempt to reduce the amount of intrinsic factor by irradiating the stomach of two of his patients and reported that they were benefited temporarily Irradiation of the pylorus and upper duodenal region was carried out in one case by Andersen Geill and Samuelsen (*166*) with *definite clinical improvement* Since that time it has been shown how ever that the intrinsic factor is secreted by the fundic portion of the stomach Any result which was attained in my opinion may have been from the general effect of the irradiation rather than the reduction in secretion of the intrinsic factor Moreover a careful study of the roent gen effects on the stomach by Stenstrom Hallock and Watson (*167*) on four patients with the disease failed to conform to the conclusions of Andersen Geill and Samuelsen

Gastric lavage as a means of removing the theoretical excess of in trinsic factor has been tried as a form of therapy in these patients with out success (*82*)

Splenectomy which has no logical basis in this disease has been per formed *without benefit* In fact it may be harmful for death has fol lowed the operation in a number of instances (*168*)

Practical Management of Patients with Polycythemia —The disadvan tages of the conventional methods of treatment are summarized by Wise man and his associates (*169*) as follows With *phenylhydrazine* the regulation of dosage is difficult secondary marrow stimulation occurs there is no control of the platelet or white blood cell levels and there is a persistent bilirubinemia *Phlebotomy* results in a hypochromic poly cythemia occasionally it causes a hypoproteinemia secondary marrow stimulation may occur and it may be unpleasant to the patient *Fowler s solution* requires a saturation dosage (which may cause gastro intestinal

country This is probably due as he suggests to inadequate treatment In some of his cases the survival time was much longer For example he cites the cases of 10 males and 10 females who lived more than 10 years with the disease and two patients still in the best of health 20 years after the diagnosis had been made

Although the opinion expressed by Wiseman and his collaborators (*169*) that "the life history of this disease when untreated particularly with respect to longevity is unknown is correct the conclusions derived from the data presented by Videbaek are suggestive

It has been assumed by Dameshek (*97*) that the course of the average treated patients with polycythemia is usually a matter of many years He assumes that the course of the disorder in some cases may be depicted as follows first a period of five years in which the hematocrit is rising and symptoms developing second an interval of five to 15 years in which the disease is fully developed but controlled by therapeutic measures third a period of two to five years in which the disease may be stationary without therapy and finally a fourth period of two to five years in which there is myelofibrosis with extramedullary hematopoiesis simulating the picture described by Jackson Parker and Lemon (*171*) as myeloid metaplasia of the spleen

The cause of death in 76 patients with polycythemia inadequately treated as given by Videbaek (*39*) and in whom none received radioactive phosphorus is as follows *hemorrhage* (cerebral intestinal epistaxis) 30 per cent *thrombosis* (cerebral and other sites) 20 per cent *chronic pyelonephritis* 18 per cent *malignancy* (three cases of carcinoma and two of leukemia) 13 per cent and *heart failure or pneumonia* 13 per cent About one half of the patients died of thrombosis or hemorrhage which Videbaek (*39*) considers to be a logical consequence of the hypertension known to be present in some cases the increase in total blood volume and viscosity the impaired circulation and the presumed hypercoagulability

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hemoglobin of 138 per cent the condition was discovered when the patient was being treated for bleeding of the gums and pyorrhea In another with a red blood cell count of 7 800 000 per cubic millimeter and a hemoglobin of 132 per cent, the disease was detected because a trace of albumin was discovered in the course of a life insurance examination and the patient was rejected It should be emphasized therefore that this disease may exist in a patient despite a feeling of absolute well being How long such changes in the blood may be present without associated symptoms is not known but it is my opinion that such an asymptomatic state cannot exist for many months without manifesting itself in one way or another

Usually when the disease is first discovered the symptoms may be relieved and the red blood cell count and hemoglobin may be reduced to approximately normal by treatment There is, however a tendency to recur hence in some patients treatment often reduces the hemoglobin to about 80 per cent and the red blood cell count to the vicinity of 7 to 7 5 millions per cubic millimeter With this there is often a microcytosis with the mean corpuscular volume in the vicinity of 65 to 75 cubic microns

There is general agreement that the spontaneous course of the disease may extend over 15 to 20 years The average duration of the condition is difficult to estimate however for several reasons In the first place, it is emphasized by Lawrence (*148*) that the average age of onset in his 172 patients was 50 4 years The average age of those who died was 67 years which is nearly the normal life expectancy for this age group Second although patients may do well as far as the polycythemia is concerned they are at the age when the common fatal diseases are prevalent such as cardiac diseases and cancer these may be the cause of death instead of polycythemia The relation between the diseases how ever is purely fortuitous Finally it is not possible to collect a large group of untreated patients in whom the disease is permitted to follow its spontaneous course over a long period of time

Probably the best series of observations which give an idea of the spontaneous course is the follow up study of Videbaek (39) who followed the course of 125 patients with polycythemia vera for various periods up to 20 years These patients received inadequate control and conse quently a too casual treatment which he believed contributed to the high mortality rate In this group he found that in 64 cases observed for 10 years the average duration of the disease in males was six years and nine years in females His observations indicate that the disorder is definitely more serious in males than in females for one half of the males succumbed in 4 5 years and one half of the females in 8 5 years This may be explained in part because the disease had its onset about four years later in the males The average duration of life after the onset in Videbaek s group is less than it is generally assumed to be in this

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is designated the generalized (acute) infantile form of Gaucher's disease (*16*). Until recently the disorder has been thought to occur principally in children and young adults but in recent years more cases which have their onset after 40 years have been reported (*12*). The disease occurs with equal frequency in both sexes.

With few exceptions the disease is found in white people but a few cases have been reported in Negroes and Orientals (*12*). A great proportion of persons affected have been Jews.

Familial Incidence.—It has been demonstrated that there is a familial incidence in more than one third of the cases which have been reported. The occurrence of more than one case in consanguinous relatives in such a high percentage of cases of a disease which is so rare demonstrates beyond the slightest question of a doubt that hereditary influences play an important role in the etiology of the condition. Five out of six children in the same family had been reported to have the disease by Brill and Mandlebaum (*3*).

An important contribution to the etiology of the disease has been made by Groen (*17*). He considers that the condition is a mutation which when once established is transmitted as a simple dominant hereditary trait. In his opinion the severity of the condition may vary considerably as the clinical manifestations may be slight or almost unnoticeable. In some patients the progression of the pathologic changes may be so slight and gradual that the disorder does not become apparent until old age. The diagnosis in such patients can sometimes be established by detecting the Gaucher cells in the sternal marrow. Such persons may be characterized as having the Gaucher trait rather than the disease. They are capable, however, of transmitting the disease to 50 per cent of their offspring. This observer believes that the disease has a tendency to become progressively severe in each succeeding generation, and after two or three generations it becomes clinically apparent early in life. Finally it becomes established in intrauterine life and death of the individual occurs *in utero* or in early infancy. Thus the condition tends to eliminate itself by allowing only the nonaffected healthy infants to survive. The author urges as a practical suggestion that in every genetic investigation of Gaucher's disease a bone marrow aspiration be performed as the best method available for the detection of subclinical cases or "carriers." A recent study by Block and Jacobson (*18*) emphasizes that the diagnosis of the condition can be established by examination of the bone marrow before the appearance of hepatomegaly or splenomegaly.

Pathology.—The disorder is characterized by the presence of many large pale cells of a distinctive structure which cause enlargement of the spleen, liver, lymph nodes and involves the bone marrow. The accumulation of these cells is regarded as the immediate cause of the

CHAPTER XXI

THE LIPOIDOSES

Gaucher's Disease—Synonyms—Metaplastic reticular and histiocytic cerebrosidosis (primary idiopathic splenomegaly, lipoid cell splenohepatomegaly, cerebroside lipoidosis)

Definition—This condition is a rare, often familial disease due to a disturbance of cellular metabolism which results in an accumulation of the cerebroside kerasin, chiefly in the reticular cells and histiocytes of the spleen, liver, lymph glands and bone marrow. Clinically it is characterized by splenomegaly, skeletal defects due to the destructive infiltration of the cerebrosidic reticulosis of the bone marrow, hepatomegaly and sometimes lymphadenopathy, pigmentation of the skin, wedge shaped thickenings of the conjunctivae near the cornea, thrombopenic purpura, leukopenia and a myelophthisic anemia.

History—The earliest description of the disease was by Phillipe Charles Ernest Gaucher (*1*) in 1882, at which time he reported that the splenic pulp in a patient whom he had observed had been entirely replaced by large pale cells which he misinterpreted as being neoplastic in nature. Hence he regarded the condition as a primary epithelioma of the spleen. The first cases in this country were reported by Bovaird (*2*) who directed attention to the presence of the characteristic large Gaucher cells in the liver and lymph nodes as well as the spleen. The name Gaucher's disease was proposed in 1913 by Brill and Mandlebaum (*3*) to replace the term primary idiopathic splenomegaly, which was obviously misleading. Epstein and Lorenz (*4*) and Lieb (*5, 6*) were the first to discover that the substance deposited in the Gaucher cells is a cerebroside which has been designated kerasin.

Excellent reviews of the literature have been published by Brill, Mandlebaum and Libman (*7*), Hoffman and Makler (*8*), Rowland (*9*), Atkinson (*10*), Tannhauser (*11*) and Reich, Seife and Kessler (*12*), Brenneman, J. (*13*), Reiss and Kato (*14*) and DeLange (*15*).

Age, Race and Sex Incidence—There are two different forms of Gaucher's disease which are determined by the ages of the persons affected. The infantile type has its onset in the first six months of life followed by death usually during the second year. The adult form may have its onset either in childhood, adolescence or adult life. The underlying cause in each instance is the same, namely, reticular cerebrosidosis. The form occurring in infancy has a serious prognosis and

the cellular cerebrosides. Further support of this view is furnished by the work of Thannhauser and his associates (*21*, *22*). A more recent publication by Ottenstein, Schmidt, and Thannhauser (*22*) supports the view of Thannhauser that the *presence of cerebrosides in large amounts in the involved organs in Gaucher's disease results from their synthesis* and storage in the cells where they are found.

Symptoms and Signs.—The following symptoms and signs are the principal ones observed in this disorder: 1, splenomegaly; 2, osseous changes resulting from destructive infiltrations of the cerebroside reticulosis of the bone marrow; 3, hepatomegaly; 4, lymphadenopathy; 5, pigmentation of the skin due to melanin or a melanin-like substance; 6, wedge-shaped thickenings of the conjunctivae; and 7, hemorrhagic manifestations associated with thrombocytopenia. Enlargement of the spleen, changes in the bone marrow and the peripheral blood, and alterations in the bones are the clinical manifestations most commonly encountered.

In the adult there are striking variations in severity. In some patients the complaints may be minor, consisting only of a vague fatigue and mild dragging discomfort in the left upper quadrant of the abdomen, and slight pains in the bones. Examination at this time usually shows a grossly enlarged spleen, and sternal aspiration reveals the typical Gaucher cells which establish the diagnosis. As previously stated by Groen (*17*), some relatives of patients with the malady may be almost asymptomatic but still have the disorder as proven by sternal puncture.

The *spleen* varies in size. In some patients it extends only one finger's breadth below the costal margin, but in others it reaches enormous proportions. Sometimes it displaces the abdominal organs and causes shortness of breath, and splenectomy may be indicated for the relief of symptoms due to mechanical reasons alone. In many instances, the splenomegaly is asymptomatic, except for a mild to moderately severe upper abdominal discomfort, but even this may be absent in some patients. The *liver* is usually not enlarged to the same extent as the spleen, and there are ordinarily no associated clinical symptoms of chronic hepatic disease. The *lymph nodes* are usually not palpable in the adult form of the disorder, but a few enlarged ones may be detected in the neck and axillae. On the other hand, in the acute infantile form, a generalized lymphadenopathy is almost always present. Next to splenomegaly, involvement of the *skeletal system* is the most common cause of the clinical manifestation of the disease. The bony changes result from infiltration of the marrow and later destructive lesions of bone which may affect any or all of the bony *structures of the body. The most important osseous complication* is destruction of the vertebrae which causes such serious consequences. Spontaneous fractures of bone have been observed.

According to Thannhauser (*16*) the following changes in the bones may be observed in the *roentgenograms*: decalcification, bone sclerosis, de-

increased size of the involved organs There are typical changes in the bones as the result of proliferation of the Gaucher cells which decalcify and rarefy the osseous structures and replace the normal marrow Gross anatomical changes are found in all bones especially the femur sternum and vertebrae The marrow is soft reddish in color and contains many small scattered white and yellow masses throughout which vary in size from a pinhead to a chestnut The resultant changes in the peripheral blood are the result of the invasion of the normal marrow and the anemia is of the myelophthisic type

Other changes which may occur are as follows (1) the pinguecula may show typical foam cells similar to those observed in the spleen (2) the skin may be pigmented as a result of deposition of melanin or a melanin derivative (3) the nervous system may be involved especially in infants with degeneration of the pyramidal cells of cerebral cortex and a proliferation of glial cells and (4) other organs such as the lungs and kidneys may occasionally contain Gaucher cells In infants the cells are frequently found in the thymus gland tonsils and lymphoid tissue of the intestine adrenals and alveolar walls of the lungs (*12*)

The Gaucher cells are large measuring from 30 to 40 microns They have one or two nuclei which often contain a nucleolus The cytoplasm stains faintly blue or grayish with the May Grunwald Giemsa stain and contains a coarse mesh as if it consisted of compressed tissue paper (*19*) The protoplasm may contain vacuoles which are artifacts produced during the fixation process and may resemble foam cells The cytoplasm does not take any of the stains well which is thought to be because it contains such a large amount of kerasin Most authors are now of the opinion that these cells are derived from the reticulum of the spleen lymph nodes and bone marrow

The cause of Gaucher's disease is unknown All agree that the underlying pathologic change is the deposition of a cerebroside known as kerasin Two views concerning the cause of the deposition of this substance have been developed One suggested by Pick in 1933 (*20*) considered that there was a disturbance in the intermediary lipoid metabolism which caused an accumulation of kerasin a galactosidase cerebroside which was ordinarily present only in the brain tissue but when present in large amounts in reticulum cells of the involved organs constituted the specific pathologic lesion of Gaucher's disease The other view is that of Thannhauser and his co workers (*21*) who demonstrated that normal serum and the serum of patients with Gaucher's disease did not contain a measurable amount of cerebroside Hence they were led to believe that kerasin was *not* deposited in the cell as a result of a general disturbance in intermediary metabolism of lipoids but was synthesized and stored in the Gaucher cells The fundamental abnormality therefore is a disturbance in the reticulum cells and histiocytes due to an imbalance of intracellular enzymes concerned with the formation and destruction of

formed elements in the circulating blood and a hyperplastic bone marrow with return to normal of the blood elements following splenectomy certainly speak strongly for an element of hypersplenism in some patients with Gaucher's disease. Further support of this is to be found in the latent jaundice which some patients exhibit and in the presence of hemosiderin in Gaucher cells. On the other hand there can be no doubt that infiltration of the bone marrow and displacement of the marrow cells undoubtedly play a significant role in the production of the changes in the blood in this disease. The place of bleeding in the production of the hematologic changes is probably not an important one.

The case of a patient with Gaucher's disease in whom there was a hyperchromic" macrocytic anemia, megaloblastic bone marrow, and free hydrochloric acid in the gastric juice is reported by Krim and his associates (24). The condition failed to respond to large doses of liver extract intramuscularly (30 units daily for 15 days) but there was a prompt and striking response to the intramuscular administration of folic acid.

Blood Chemistry.—There are no characteristic chemical changes in the blood of patients with this disorder. There has been no case reported with a lipemia; the total cholesterol content is normal or a low normal and the percentage of cholesterol esters is within normal limits. It has not been demonstrated that cerebrosides are present in measurable quantities in the blood serum of patients with this disease (25). Despite the extensive infiltration of the liver with Gaucher cells, usually all liver function tests are normal. The calcium and phosphorus values are normal. There is often a slight increase in blood bilirubin (from 1.0 to 2.0 milligrams per cent) which may be due to increases in red blood cell destruction.

Diagnosis.—The diagnosis of Gaucher's disease is suggested in the fully developed case by the presence of an enormous enlargement of the spleen with a moderate increase in the size of the liver and the pigmentation of the skin. When these signs are associated with a moderate anemia, a leukopenia and a thrombopenia with a hemorrhagic tendency, then a sternal puncture is at once suggested. This should clinch the diagnosis for in each instance in which the patient has the disease the typical Gaucher cells should be demonstrated.

Treatment and Prognosis.—The prognosis depends to a great extent on the age at which the manifestations of the disorder appeared. If this occurred in the first decade, the outlook is poor. In the acute generalized type of the disorder which occurs in infancy, the duration of life commonly does not exceed a few months. On the other hand, if the symptoms are delayed until the third or fourth decade, the patient may survive until old age with relatively mild symptoms.

Patients with the adult form of the disease rarely succumb to the disease itself but to some intercurrent infection. Tuberculosis has been

formities in the outlines of bones, especially in the femur and the vertebrae Occasionally osteosclerotic changes are noted in bones especially the radius and ulna

It is not unusual to have joint complaints in patients with this disease which are attributable to involvement of the bone marrow Objective changes are not likely to occur however, until there are extensive advanced destructive osseous changes *Pigmentation* possibly due to a true melanin, is present in the form of cloasma like patches of a brownish tan color and may occur over the exposed portions of the body such as the hands arms, and face The *eyes* in some cases show the characteristic *wedge shaped brownish pinguecular of the conjunctiva which* some think is a specific sign of the disease Certainly when these are observed in a patient who has an enlarged spleen the diagnosis of Gaucher s disease should be given serious consideration

Changes in the Peripheral Blood in Patients with Gaucher s Disease — The hematologic changes in patients with Gaucher s disease are usually a mild to moderate anemia of the normocytic normochromic or hypochromic type a *slight leukopenia* and a *moderate thrombocytopenia* In 16 of the 20 cases reported by Reich Seife and Kessler (*12*) the hemoglobin of the circulating blood was 11 grams per 100 cc (70 per cent) or less Three patients with the lowest hemoglobin levels had readings of 6 5 6 6 and 8 2 grams per 100 cc The *red blood cell counts* in 15 of these patients were below 4 0 millions per cubic millimeter The *white blood cell counts* were uniformly below 6000 per cubic millimeter, the lowest in the 20 patients being 1400 per cubic millimeter The differential counts were normal or showed a relative neutropenia In all 20 patients with one exception there was a reduction in the *blood platelets* below 200 000 per cubic millimeter the average being about 100 000 to 120 000 and the lowest 82 000 per cubic millimeter

The cause of the blood changes appears to be two and possibly three factors as follows (1) the infiltration of the bone marrow and impaired production of erythrocytes, leukocytes and platelets (2) effect of hyperactivity of the spleen which results in the production of the blood picture of "hypersplenism" and (3) the loss of blood due to the increased tendency to bleed

The role of *hypersplenism especially in the production of thrombocytopenia* is discussed by Davis Genecin and Smith (23) who refer to the literature on this subject They present a case of Gaucher s disease in which all of the blood values were normal except a reduction in the blood platelet count to 62 000 per cubic millimeter A bleeding tendency was one of the patient s complaints Removal of a spleen laden with Gaucher s cells produced a dramatic remission with a return of the blood platelets promptly to normal Apropos of this case it may be said that in patients with an enlarged spleen a reduction in one or all of the

The disease is regarded by Thannhauser as a constitutional probably congenital familial systemic disorder of the cellular metabolism in the reticulo-endothelial cells and histiocytes" He believes that there is a disturbance of the lipid metabolism in these cells which results in the accumulation in the cases of Niemann Pick's disease of sphingomyelin Since the glands of internal secretion may be involved and in some instances destroyed it is to be expected that some of these patients may display evidences of endocrine disorders as a secondary effect

Pathology —The pathological changes may be summarized as follows there is striking involvement of the liver and spleen generalized enlargement of the lymph nodes the lungs and bone marrow No tissue in the body however is immune to involvement with the Niemann Pick cells As previously mentioned this widespread distribution is a distinguishing feature from Gaucher's disease

The Niemann Pick cell is a large pale oval or round cell which varies in diameter from 20 to 50 microns It has an abundant cytoplasm with bright granules When the fat is dissolved by the ordinary fixing reagents the cytoplasm is transformed into one which has a fine reticular network giving a "foamy or vacuolated appearance Hence from this appearance it derives the name "foam cells

Symptoms and Signs —The following clinical manifestations of the disorder may occur hepatomegaly splenomegaly lymphadenopathy diffuse pigmentation of the skin and an irregular distributed bluish black discoloration of the mucous membranes of the mouth gastric disturbances mental deterioration and emaciation and extreme cachexia which usually culminate in the death of the patient within the first two years of life

Blood Examination —There is often a moderate anemia of a normocytic or microcytic and normochromic type Leukopenia may be present although some cases have a moderate leukocytosis The platelets may or may not be diminished The most distinctive finding is the occasional presence of foam cells in the circulating blood (27) This is in contrast to Gaucher cells which are not found in the blood

Blood Chemistry —According to Thannhauser (16) the cholesterol is not increased or is only slightly increased in the circulating blood The total fat is slightly above normal and the blood serum may be slightly lipemic

Prognosis and Treatment —The disease is uniformly fatal and resists all forms of therapy Death usually occurs within the second year of life

Schuller Christian Syndrome—**Synonyms** —Osseous xanthomatous granuloma (defects in the membranous bones of the skull exophthalmos and diabetes insipidus)

This condition is considered by Thannhauser (16) to be one of the primary essential xanthomatoses due to a faulty metabolism of cholesterol and cholesterol esters within the cell This author considers that the

important in the past in this connection The anemia and thrombocytopenia have also been of importance in determining the prognosis

There is no specific treatment known to influence favorably the underlying cause of the disease *Splenectomy* should be given serious consideration for at least two reasons 1 the enormous size of the spleen may itself be an indication for its removal for the relief of mechanically produced symptoms and 2 if there is an anemia of a normocytic normochromic type a thrombocytopenia or a leukopenia or a combination of these and a hyperplastic bone marrow there is some reason to believe that the blood condition may be greatly improved by splenectomy If the patient has a macrocytic anemia folic acid should be given a trial in doses of 10 milligrams orally twice daily Iron is indicated if there is hemorrhage and the anemia is hypochromic in type Other forms of treatment including ray therapy applied to the spleen are of little avail

Niemann Pick s Disease—Synonyms—Metaplastic reticular and histiocytic sphingomyelinosis lipoid cell sphenohepatomegaly Niemann Pick type lipoid histiocytosis essential lipoid histiocytosis phosphatid lipoidosis

Definition—The condition is an uncommon familial congenital disorder in which the histiocytes and reticular cells of *all organs* in the body may have a disturbance of cellular lipoid metabolism According to Thannhauser (*16*) the histiocytes and reticulum cells of *all organs* may be involved whereas in Gaucher s disease only the lymphohemopoietic system liver spleen lymph nodes and bone marrow are primarily *affected This observer also states that there is an accumulation of* diaminophosphatide (sphingomyelin) in these cells It is his opinion that the condition results from dysfunction of the intracellular enzyme system which causes the sphingomyelin to be formed and deposited in the cells in which it is found

History—In 1914 Niemann first drew attention to this condition by publishing *the case of an infant 18 months of age who had a condition* similar to Gaucher s disease The main difference was that there was an involvement of the cells throughout the body instead of the usual limitation of the process to the spleen liver lymph glands and bone marrow as in Gaucher s disease

It was Pick (*25*) who differentiated the condition from Gaucher s disease and established it as a new clinical and pathological entity The studies of Klenk (*26*) showed initially that sphingomyelin was the lipid which was involved in this condition

Etiology—There is a greater incidence in females in the reported cases the proportion being five to one The disease occurs almost exclusively in infants and none of the patients have survived longer than the second year In recent years however several cases have been reported in adults It is said to occur more frequently in the Jewish race as the proportion of Jewish to non Jewish infants reported is three to one (*11*)

The diabetes insipidus is evidenced by the presence of polydipsia and polyuria which is regularly present in patients with this syndrome

It is known that any one of the three outstanding symptoms of this disorder may occur singly or each one may be associated with xanthoma disseminatum With the simultaneous occurrence of all three of the features of the condition its nature is at once apparent It is mentioned by Thannhauser (*16*) however that if only the bone defects develop especially in older children or in adults differentiation may become difficult because the bone findings may become confused with other conditions He mentions the following which should be considered Gaucher s disease Niemann Pick syndrome the lymphoblastomas multiple myeloma erythroblastic anemia chloroma osteoitis fibrosa cystica Recklinghausen s disease and isolated bone cysts of unknown etiology

Prognosis and Treatment —In patients with the Schuller Christian syndrome as in the other associated essential xanthomatoses of the normal cholesteremic group the course of the disease is prolonged Since the disturbance is now considered to be one of intra cellular metabolism of lipids there is no form of treatment which is known to correct the fundamental abnormality and hence any treatment must necessarily be symptomatic It is advised by Thannhauser (*34*) that it is not necessary to observe strict restrictions in diet as the blood cholesterol is not importantly elevated Likewise he considers that medication with desiccated thyroid is not indicated It has been pointed out by Sosman (*35 36*) that the roentgen ray exerts a favorable effect on the osseous xanthoma of this group This is also true of the involvement of the lymph nodes but not for the lesions of the skin

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condition is a subdivision of the normo cholesteremic group and the etiology of the foam cells containing the lipids is not different from the other forms

History —Apparently this syndrome was first recognized by Hand (28) in 1893 who erroneously attributed it to tuberculosis Later in 1905 Kay (29) reported a similar case which he interpreted as one of acquired hydrocephalus with atrophic bone changes In 1915 Schuller (30) published a report of a 16-year old patient with the same three outstanding clinical features Christian in 1919 (31 32) observed the syndrome in a five year old girl who apparently recovered To Rowland (33) should be accorded the credit for having proved that this condition belonged to the group of essential xanthomatoses

Etiology —The disease usually occurs in infants and young children but occasionally it has been observed in adults Thannhauser and Magendantz (34) report the case of a 51 year old male with the syndrome Males are more likely to have the disease than females A family tendency has been observed as in other forms of xanthomatoses The underlying cause of the condition is completely unknown

Pathology —The bone defects of the skull usually involve the inner and outer tables and as the disease progresses the entire vertex and base of the skull may show defects Xanthomatous nodules may appear in the dura and enlarge as rubbery yellowish masses which produce osseous defects by replacing bone When they arise at the base of the skull they encroach on the vicinity of the pituitary gland which probably accounts for the syndrome of diabetes insipidus Such tumor like growths may also extend forward into the orbits displacing the eyes in such a way as to produce exophthalmos Xanthomatous lesions may be present elsewhere in the body namely the lymph glands the skin liver dura and long bones

Histologic examination of the xanthomatous areas show that they are formed chiefly by histiocytes containing lipid and foam cells There are proliferative and granulomatous phases in which an accumulation of eosinophilic leukocytes is observed in addition to other cells In some instances there is a connective tissue replacement

Symptoms and Signs —The three characteristic features of the syndrome are (1) defects of the membranous bones (2) exophthalmos and (3) diabetes insipidus The bony defects are usually discovered because of the deformity of the skull which is ordinarily restricted to the area covered by the scalp The roentgen ray discloses the striking defects in the bones of the skull and in some instances lesions also involving the superior and inferior maxillae scapula ribs vertebrae pelvis and long bones The osseous lesions are usually not productive of pain

The exophthalmos is bilateral and is considered to be due either to the granulomatous like masses in the orbits or to destruction of bone processes in the orbital regions

CHAPTER XXII

STERNAL PUNCTURE

Nature of the Information Which May Be Obtained from Sternal Puncture.—It is not to be expected that sternal puncture will in any way replace a thorough study of the patient and the use of other accepted diagnostic procedures. As so often happens with the introduction of any new and useful diagnostic technic, it is sometimes employed improperly to the exclusion of other methods of proven worth. Conclusions regarding the usefulness of sternal puncture are given by Propp and Schwind (*1*) and in general I am in accord with these. In a study of 140 cases they found that the procedure gave information of clinical value in 65 per cent of the instances in which it was performed. Furthermore, the actual diagnosis was made in 16.2 per cent of their patients when it was impossible by any other method except examination of the sternal marrow. In other words, sternal puncture often furnishes useful information which corroborates other data of a diagnostic nature, but only in a relatively small proportion of cases does it alone provide specific data which are of a definite diagnostic nature. These authors consider that such specific diagnostic data are obtainable in the following conditions:

1. Leukemia, especially the acute and chronic subleukemic types.
2. In the presence of megaloblastic marrow, which is found characteristically in pernicious anemia in relapse, but also in closely allied states such as sprue, certain deficiencies of the "extrinsic factor," and gastro-intestinal disturbances (total gastrectomy, stricture and anastomosis).
3. Agranulocytosis in the stage of maturation arrest.
4. Neoplasms: multiple myeloma and metastatic malignancies.
5. Lipoid histiocytosis.
6. Malaria.
7. Leishmaniasis (kala azar).

In my opinion two other conditions should be added to this list of diseases in which sternal marrow examinations are exceedingly useful. One is *idiopathic thrombocytopenic purpura* and the other is *hypersplenism*. It is certainly true in my experience that the former condition is always associated with a normal or even increased number of megakaryocytes in the marrow and I would not recommend splenectomy or anticipate a favorable response to cortisone or ACTH therapy unless these precursors of the circulating blood platelets were present in the marrow. The marrow in hypersplenism is characteristically hyperplastic and this

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his method of introducing a trocar into the upper epiphysis of the tibia or the lower end of the femur and aspirating two drops of marrow. He advocated this method as one which was superior to that of obtaining material by splenic puncture in the diagnosis of the anemia of children with Leishmania. Even though the date of Pianese's work is later than that usually cited in the literature the credit for first *aspirating* material from the bone marrow in humans for diagnostic purposes should be given to him. In the preceding year Ghedini (*7, 8, 9*) had studied the marrow obtained *by trephining* the tibia in the upper third. This procedure was subsequently employed by Zadek (*10*) in 1921 and Peabody (*11*) and others as a means of study in the various stages of pernicious anemia.

An excellent bibliography relating to the developments of the method of sternal puncture and the evaluation of the information which can be obtained from such a study is to be found in the comprehensive article by Segerdahl (*6*).

In 1923 Seyfarth (*12*) introduced the method of trephining the sternum for the reason that the marrow of the tibia is usually hypoplastic whereas that of the sternum is more cellular and reflects the activity of the bone marrow more accurately. While this procedure is of value, for the material can be studied in both sections and films, nevertheless the patient was often impressed unfavorably with the surgical nature of the procedure and repeated specimens were not always obtainable. Moreover, although the resulting scar was small it was undesirable, especially in women. All of these objections were overcome when Arinkin (*13*) introduced his simpler method of obtaining sternal marrow by means of aspiration of the material through a modified spinal puncture needle.

Value of Sternal Biopsy and Puncture.—It had long been known that the state of the peripheral blood does not necessarily reflect the condition of the bone marrow, although in many instances this is true. For many years the clinical hematologist had hoped for some more simple procedure which would give him more specific information concerning the nature of the bone marrow during the life of the patient and one which could be easily repeated at intervals. Since the introduction of sternal biopsy by Ghedini in 1908 and that of sternal puncture by Arinkin in 1927, valuable information relating to the state of the marrow has been made available. It is thought by some that specimens obtained by sternal trephining are superior to those aspirated through a needle. The only advantages of the biopsy, which in my opinion are far outweighed by its disadvantages, are that the relations of the cells are well preserved and the sample obtained is composed entirely of bone marrow. Rarely in my experience in recent years has bone marrow biopsy been thought to be necessary.

When sternal aspiration is employed it is recognized that the specimen is diluted to a certain extent by blood and hence this must be taken into account when the findings are evaluated. During the past few years

finding with a reduction in one or more of the circulating elements of the blood and an enlarged spleen, except in idiopathic thrombocytopenic purpura, constitute the diagnostic triad of hypersplenism If the marrow were not hyperplastic I would not recommend splenectomy on the basis that the patient had hypersplenism and would be benefited by the operation

It should not be assumed that the conditions listed above are invariably associated with a highly characteristic picture In some instances the changes may be atypical and confusing In others, the marrow may appear to be entirely normal even when other information indicates clearly that certain blood diseases are present One obvious explanation of this is that there may be an error in sampling the marrow Furthermore, it is known that treatment such as the administration of liver extract to patients with pernicious anemia, may be responsible for extremely rapid transformations in the marrow It should be kept in mind therefore that positive findings in the bone marrow as a rule are more reliable from a diagnostic standpoint than negative ones although in some instances the latter are of great importance

It *is considered by Propp and Schwind (1) that in certain disorders* there is a non specific picture in the bone marrow and while such changes are not conclusive from the standpoint of diagnosis they nevertheless give useful information The following diseases are listed in this group polycythemia, hypochromic hemolytic and aplastic anemias and myelophthisic anemia which occurs in such conditions as Hodgkin s disease and reticulosis

In my own opinion sternal puncture is an exceedingly valuable diagnostic procedure in all patients with any type of blood disease In a few conditions it is by itself diagnostic but more often it is confirmatory of the clinical diagnosis which has been suggested and supported by other accepted diagnostic studies A real danger which is associated with the interpretation of the bone marrow obtained by sternal puncture is that *too much reliance may* be placed on it from a diagnostic standpoint when the findings are reported by inexperienced observers

A most comprehensive and informative article on the normal and pathologic physiology of the bone marrow has been written by Zuelzer (2) One dealing with the diagnostic value of bone marrow studies in infants and children has been published by Poncher (3)

History —Apparently the earliest attempt to study the bone marrow in a living animal was that of Wolff in 1903 (4) who observed the opened marrow cavity of the femur and tibia

It has been previously stated that Pianese (5) was the first to aspirate the bone marrow in humans in 1903 A *search through* the literature indicates that this investigator introduced bone marrow puncture in 1909, rather than six years before (6) In this publication he described

has not been previously determined although it has been known to exist By the technic used they calculated that the dilution with circulating blood varies from 40 to 100 per cent It is emphasized therefore that obviously the cell count of the marrow is not significant when the total number of cells is considered Information obtained by doing a differential count on the marrow aspirated however is more accurate and furnishes acceptable information

The Sternum Iliac Crests and Spinous Processes as Sites for Obtaining Bone Marrow —There have been three sites utilized for aspiration of bone marrow all of which yield essentially the same type of material The original technic of aspirating sternal marrow as introduced by Arinkin in 1927 has been the one chiefly employed since that time and found to be satisfactory in all respects It is advisable that this location be utilized routinely It is however useful to have other sites available as occasionally the results of sternal aspiration are unrevealing and more pertinent information may be secured by obtaining marrow from other locations Bone marrow may be secured by puncture of the iliac crest as originally advocated by Van den Bergh and Blitstein (18) and from the spinous processes as employed first possibly by Katsunuma in Japan in 1941 and later adopted by Nakato of the Tokyo Imperial University (19) There is no uniform agreement concerning the priority of this procedure as it has been stated that the first spinous process puncture was performed by A and C Heidenreich (20) and was later more extensively used by de Weerdt (21)

In an article by Rubinstein published in 1948 (22) he gives the details of the technic employed in iliac crest puncture He concludes that the bone marrow may be obtained easily safely and repeated from this site In his opinion the diagnostic advantages of iliac over sternal marrow aspirations are observed in infiltrative disorders as in neoplastic involvement and in some patients with multiple myeloma In a more recent article this same observer (23) reported that in studying 100 consecutive patients with advanced metastatic malignant disease neoplastic cells were observed considerably oftener in the iliac than in the sternal marrow when the aspirations were performed at the same time According to these authors both sternal and iliac aspirations were positive in 15 patients both sternal and iliac aspirations were negative in 59 patients iliac aspiration alone was positive in 22 patients and sternal aspiration alone was positive in four patients Of the 26 patients who showed x ray evidence of bony metastases six had neoplastic cells in smears of marrow aspirates in only one of these six however were these cells also present in the marrow from the sternum They conclude from their observations that the iliac marrow is superior to the sternal marrow as a site for aspiration of neoplastic cells

however, so much experience has been obtained by sternal puncture that interpretations are now reliable in the hands of the experienced hematologist despite the contamination of the sample with peripheral blood. The operation of sternal puncture is so simple that it can be performed a number of times if necessary in the same patient without undue discomfort, and in all patients in whom the diagnosis of the blood condition is obscure.

It is known that the marrow of the sternum remains active throughout life and that it is one of the most sensitive areas to respond to stimuli which cause changes in the marrow. It has been claimed (*14*) that simultaneous puncture of several bones (ribs, sternum, pelvis) yields similar information. Evidence has been secured by von Domarus (*15*) which indicates to him that there is some irregularity in the distribution of the cells in the sternum, and there is some confirmation of this at necropsy.

In recent years there has been a tendency to study the aspirated sternal marrow quantitatively and to establish certain fixed ratios between the various types of marrow cells. Reich (*16*) has emphasized, however, that such exactness quantitatively is not to be expected. This is because the material aspirated from the sternum is not homogeneous like the blood, and hence it cannot be studied with the same degree of accuracy. They conclude that it is possible to make *qualitative studies* on this material just like a tissue, and, to some degree, rough quantitative determinations. They conclude their article with the statement that statistical analysis indicates that *quantitative* determinations on aspirated marrow samples are inaccurate, but that *qualitative* studies are invaluable in establishing hematologic diagnosis. A further statement in their article is of such importance that it is quoted verbatim, namely, "Examination of the stained marrow preparations requires the attention of an expert hematologist, whose judgment must naturally be tempered by a thorough clinical examination of the patient. In recent years this diagnostic procedure has been employed in a great many instances and has proved to be exceedingly helpful. On the other hand, it is a relatively simple matter to obtain the marrow sample but, as previously stated, one which requires an extensive experience in order to interpret the findings correctly."

Composition of the Normal Marrow Aspirated from the Sternum.—The material obtained by this method is composed of marrow from the sternal cavity diluted with a variable amount of blood. For this reason it is advisable to withdraw into the needle only a small amount of marrow. Two tenths to five tenths of one cubic centimeter is a sufficient quantity. By using P 32 labeled red blood cells a study has been made by Berlin, Hennessy, and Gartland (*17*) to estimate the degree of dilution of the sternal aspirate by the peripheral blood. The magnitude of this dilution

the technic of marrow aspiration and the handling of material after aspiration and especially on the acceptance of more uniform criteria of cell identification and nomenclature Tentatively these authors recommend that the total 95 per cent range for the nucleated cell count when 0 5 to 1 0 cc is aspirated be considered as varying from 10 000 to 100 000 per cubic millimeter, and that the weighted mean be 35 000 per cubic millimeter When 0 05 to 0 5 cc of aspirated material is employed they suggest that the 95 per cent range be considered as 10 000 to 160 000 per cubic millimeter with a weighted mean of 15 000 per cubic millimeter The great range of these figures indicates clearly that one should not attempt to be too precise in making a statement about the number of cells present but be content with a rough estimation as suggested by Scott (25)

Technic of Sternal Puncture—The technic of accomplishing a sternal puncture successfully is a very simple matter and does not result in any important inconvenience to the patient although some slight pain is always associated with the procedure Two deaths occurring during the process of performing a sternal puncture have been reported by Bardhan (27) Death in both instances was due to rupture of the right ventricle following a prick by the needle causing hemopericardium and arrest of the heart

The puncture is accomplished with a short (about 3 to 4 cm) number 18 gauge lumbar puncture needle which may be equipped with a finger grip For a number of years we have employed such a short needle with beveled obturator The needle is inserted in the middle of the body of the sternum at about the level of the second intercostal space This site may be readily located by using the sternal angle which indicates the level of the second rib as a guide It is advantageous to hold the lateral margins of the body of the sternum between the thumb and forefinger of the hand which is not used for the puncture as a means of approximating the center of the sternum This is of some importance because if the puncture is made too far laterally the marrow cavity may not be entered

The puncture is made following novocaine infiltration of the skin subcutaneous tissues and periosteum of the sternum The outer table of the sternum is passed through at an angle of about 45 degrees with a firm boring motion and a "give" may be felt in some instances when the needle enters the marrow cavity When it is thought that the marrow cavity is entered the obturator is removed and an attempt is made to aspirate a small amount of material If this is not successful then the needle should be pushed a short distance further and the process repeated until sternal marrow is obtained which has the gross appearance of normal blood In most instances there is a certain amount of sharp but transient pain when the marrow is aspirated from the sternum

It is advisable to withdraw only about 0 2–0 5 cc of marrow fluid as this is a sufficient quantity for all studies and the collection of a greater

The technic of spinous process puncture and a review of the work of previous observers is given by Loge (*19*). He states that aspiration of marrow from the spinous processes is a simple procedure and concludes that marrow samples obtained simultaneously from the sternum and spinous processes showed essentially the same changes in 25 patients. The material was aspirated from the spinous processes of L_3 and L_4. In the opinion of this investigator the spinous process puncture provides the clinician with another approach in obtaining active marrow by aspiration which appears to be as useful and equals the sternal route in simplicity.

The different sites for marrow aspiration serve a most useful purpose when a dry tap results from a sternal puncture, or when the diagnosis suggested by the clinical manifestations and other laboratory data is not substantiated by the sternal marrow aspirate. Under these circumstances the first additional study to do is to repeat the sternal puncture or to employ one of the other optional sites. If these are all unrevealing then the possibility of a trepine biopsy on the sternum should be considered.

In discussing the usefulness of multiple sites for marrow aspiration Rheingold, Weifuse and Dameshek (*24*) emphasize that they have the following advantages: by using a number of spinous processes it is possible to obtain a series of observations on the marrow which is advantageous in following the course of the disease and in guiding therapy; when the diagnosis is in question and particularly when a hypocellular marrow is obtained the employment of multiple sites is often helpful; when irradiation may influence the sternal site it is useful to have other areas available; in children they believe that the spinous process and iliac crest are often the preferred sites.

The Number of Cells in the Marrow.—It is obviously desirable to determine as accurately as possible the degree of cellularity of the marrow, but, as previously emphasized, it should not be expected that this can be expressed precisely in figures. It has been shown that the range in the numbers of nucleated cells in the marrow is so great that any figures which have been given as the normal range are useless. Scott (*25*) states that despite the inaccuracies inherent in a cell count there is little doubt that the degree of cellularity of the puncture fluid is of significance in most cases and does reflect roughly the number of cells in the sternal marrow provided a standard technique is used. He grades the cellularity into low (approximately that of a normal blood film), medium (that of a healthy marrow), and high. It is his opinion that to strain after greater precision is to attempt to endow the method with an accuracy it cannot possess.

It is stated by Osgood and Seaman (*26*) that before specific recommendations can be made for aspirated marrow as to normal standards it is necessary to await further studies and a more general agreement on

TABLE XLIII

CELLULAR CONTENT OF THE NORMAL BONE MARROW

Type of Cell	Range in Per Cent (Wintrobe)	Average Per Cent (Wintrobe)	Range Per Cent (Plum)	Average Per Cent (Plum)
Myeloblasts	0.3– 5.0	2.0	1.0[illegible]– 1.86	1.42
Promyelocytes	1.0– 8.0	5.0	1.02– 3.61	2.38
Myelocytes: Neutrophilic	5.0–19.[illegible]	12.0	2.72– 9.24	6.12
Eosinophilic	0.5– 3.0	1.5	0.56– 2.14	1.60
Basophilic	0.0– 0.5	0.3	[illegible].00– 0.39	0.07
Metamyelocytes	13.0– 32.0	22.0	5.2[illegible]–11.[illegible]	7.93
Polymorphonuclear Neutrophils	7.0–30.0	20.0	22.18–60.58	35.[illegible]
Polymorphonuclear Eosinophils	0.5– 4.0	2.0	0.40– 3.16	1.51
Polymorphonuclear Basophils	0.0– 0.7	0.2	[illegible].00– 0.32	0.09
Lymphocytes	3.0– 17.0	10.0	3.74–10.78	6.32
Plasma Cells	0.0– 2.0	0.4	0.00– [illegible].40	0.18
Monocytes	0.5– 5.0	2.0	0.20– 1.54	0.77
Reticulum Cells	0.2– 2.0	0.[illegible]	[illegible].36– 2.20	1.07
Megakaryocytes	0.03– 3.0	0.4	0.0[illegible]– 0.4[illegible]	0.19
Pronormoblasts	1.0– 8.0	4.0	0–0	0
Normoblasts	7.0–32.0	18.0	[illegible]3.54–43.42	34.81

Percentages taken from Wintrobe and Plum
(Courtesy Lea & Febiger and *Acta med. Scandinavica.*)

trephining the sternum and not by aspiration but occasionally this is the case.

If a specimen obtained by trephining the sternum is desired, the simple procedure devised by Turkel and Bethell (29) is the method of choice. The device employed consists of two needles with stylets, an outer guiding needle of 14 gauge and an inner trephine needle of 17 gauge. As described by these authors "The external guiding needle should be 2 to 3 cm. in length. One end of this needle has a sharp beveled point while the other end has a hollow head with a slot into which the projection of the head of the stylet fits. This arrangement keeps the point of the needle and the point of the stylet at the same cutting angle. The purpose of the guiding needle is to cut (split) through the skin and subcutaneous tissue without incising them and to direct the inner trephine needle to the desired position." For the details of their technic, reference should be made to their original article (29). It is therefore possible to obtain a small specimen of marrow with no more effort than that used in securing marrow by aspiration and with only slight discomfort. If aspirated material is also desired, then the area anesthetized should be large enough to permit the introduction of an aspiration needle one cm. below the point of introduction of the trephine.

The Normal Bone Marrow.—Although it is not possible to make accurate cell counts from the bone marrow, valuable information may be obtained by examining from 500 to 1000 consecutive cells in marrow films. Even when this is done, however, too much stress should not be placed

amount means an increased dilution with the circulating blood which impairs the value of the examination somewhat Smears are made by ejecting the material from the needle of the syringe onto properly prepared glass cover slips It is usually advisable to make 10 to 12 smears from each specimen for despite careful technic perfect smears are difficult to obtain This is because it requires considerable experience to estimate the optimum size of the drop of blood and marrow mixture and because the material always contains a certain amount of fat The films thus prepared are then stained with Wright s or Giemsa s stain

The method of staining films as used at the Simpson Memorial Institute is as follows

1 Cover the marrow film with undiluted Wright s stain for one minute

2 Dilute with fresh redistilled water (pH about 6 6) in proportion of two drops of water to one drop of stain The amounts of stain and water may be varied depending on the quality of the stain The red blood cells should be stained pink and the nuclei of the white blood cells purple After three minutes flood off the precipitate from the surface with redistilled water Let the water stay in contact only until the stain is light pink

3 Cover the stained film with redistilled water add an equal amount of Wright s stain mix and stain for three minutes flood off precipitate and dry

Technic of Bone Marrow Examination Recommended by Propp —A refinement in the technic of obtaining marrow aspirate and preparing it for a more comprehensive study has been introduced by Propp (*28*) By this method the original Arinkin technic of sternal puncture has been modified to include iliac spinous process and tibial marrow aspirations *A dilute solution of sodium heparin is placed in the aspirating syringe* which prevents clotting and provides for a more complete utilization of the material obtained from the marrow cavity Three specimens are prepared No 1 smears made directly from the needle No 2 the marrow bit or particle smears No 3 smears made from the concentrate obtained by centrifuging If desired a fourth preparation may be made in the form of a fixed specimen There can be no doubt but what these additional studies would be of great assistance in providing more reliable information on which a diagnosis could be based

Biopsy of the Bone Marrow by a Simple Instrument —As previously mentioned marrow obtained by sternal puncture may not be representative of the quantitative relationship between cellular elements within the marrow in certain conditions, as myelosclerosis it may not be possible to obtain material from the marrow cavity and in disorders characterized by a hypoplastic state of the marrow as aplastic anemia the material secured by aspiration is of uncertain significance It must be admitted that only rarely is positive diagnostic information obtained by actually

the article dealing with the normal marrow by Plum (31, 32). The latter publication is a most comprehensive review of the literature which is presented along with the author's own studies on the cellular composition of the bone marrow.

There are several points which should be kept in mind when studying the normal marrow. First, the degree of cellularity which has been previously mentioned. It is probably best to indicate this approximately by stating that it is below normal, normal, or increased. Second, in health the proportion of white blood cells of all types to nucleated red cells is in a ratio of five to one to three to one. In anemias this ratio is much lower and may be reversed. It is also known that normally the

TABLE XLIV

	Weighted Mean	*95 Per Cent Range*
Myeloblasts	1.25	0.0– 2.4
Promyelocytes	1.50	0.0– 3.0
N. Myelocytes	15.0	8.0–27.0
N. Metamyelocytes	15.5	8.0–23.0
N. Staff Cells	9.0	6.0–12.0
Polymorphonuclears	22.0	15.0–28.0
Eosinophils	3.0	1.0– 5.0
Basophils	0.2	0.0– 0.4
Lymphocytes	18.5	7.0–30.0
Monocytes	2.0	0.0– 4.0
Erythroblasts	12.0	3.0–21.0

Standards for Differential Count of the Bone Marrow (Osgood and Seaman (26))
(Courtesy *Physiological Reviews*.)

proportion of granular to non-granular white cells is about four to one. Furthermore, it should be kept in mind that many observers do not believe that megaloblasts are present in normal marrow, and certainly all agree that, if present, their numbers are exceedingly small. In pernicious anemia and allied macrocytic anemias, however, megaloblasts make up a considerable percentage of the nucleated cells and constitute the chief change in the marrow in that disease.

Normally in bone marrow the cells multiply by karyokinetic division and ordinarily one sees mitotic figures to a certain extent. It is of importance to estimate the number of mitotic figures, for when they are increased it may be indicative of some pathological condition. It is stated by Japa (33) that in each 1000 nucleated cells about 15 normally show mitotic figures. In the leukoblastic system 97 per cent of the dividing cells consisted of myelocytes and 3 per cent of myeloblasts. In the erythroblastic system 91 per cent of the dividing cells were late and 9 per cent early erythroblasts.

on minor alterations The variation in the number of cells and the types of cells which occur in the normal marrow are questions which are not settled precisely at present, although our information is adequate enough to be of assistance in assesing the findings of material removed by sternal aspiration

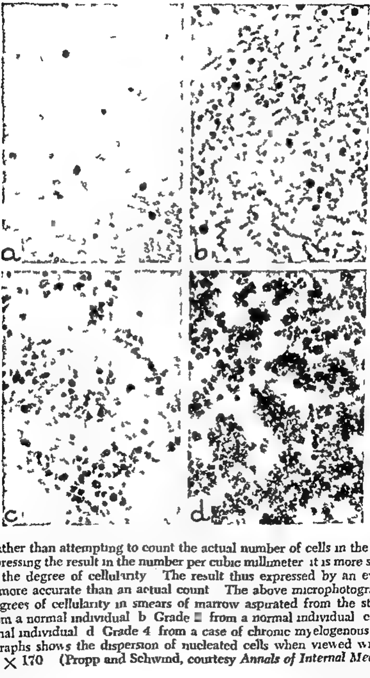

Fig 76 — Rather than attempting to count the actual number of cells in the bone marrow and expressing the result in the number per cubic millimeter it is more satisfactory to estimate the degree of cellularity The result thus expressed by an experienced observer is more accurate than an actual count The above microphotographs show different degrees of cellularity in smears of marrow aspirated from the sternum a Grade 1 from a normal individual b Grade 2 from a normal individual c Grade 3 from a normal individual d Grade 4 from a case of chronic myelogenous leukemia The photographs shows the dispersion of nucleated cells when viewed with the 16 mm lens × 170 (Propp and Schwind, courtesy *Annals of Internal Medicine*)

Table XLIII providing data on the cellular content of the normal marrow is based upon information given by Wintrobe *(30)* and that from

cell of the entire hemopoietic series In a hyperplastic marrow due to any cause such cells are increased in number Hence they are observed in the marrow of patients with pernicious anemia during relapse in normoblastic marrow hyperplasia and in leukemic marrow In general however it may be said that in patients with pernicious anemia the characteristic finding in the films is the presence of many promegaloblasts and basophilic megaloblasts which frequently show mitotic figures

There is also a leukoblastic reaction of a non specific kind as indicated by an increase in the number of promyelocytes and myelocytes present This does not correlate on first thought with the leukopenia and relative lymphocytosis of the peripheral blood but the obvious explanation is that although the leukopoietic tissues in the bone marrow show signs of hyperactivity for some unknown reason the leukocytes are not released from the marrow at an increased rate It is interesting to note that the macropolycyte with hypersegmentation of the nucleus is often seen in the bone marrow of patients with pernicious anemia as well as the peripheral blood

The megakaryocytes are characteristically reduced in number

The Bone Marrow of Patients with Pernicious Anemia in Remission — With the beginning of a spontaneous remission or one induced as a result of therapy there are very prompt and characteristic changes in the bone marrow The earliest detectable change which is said to begin within 24 hours is an increase in the rate of maturation of the megaloblasts This is shown by a decrease in the number of promegaloblasts and basophilic megaloblasts which promptly diminish in number and finally disappear from the marrow They are replaced by polychromatic and orthochromic megaloblasts and this change is followed by the appearance of a large number of normoblasts The increase in the cells reaches a maximum at the time the reticulocytes have attained their peak in the peripheral blood Simultaneously with the alterations in the red blood cell forming elements there is a return of the granulopoietic cells to normal as indicated by a rapid maturation of the abnormal myelocytes and other immature white cell forms which are replaced by normal cells

Changes in Other Macrocytic Anemias —In addition to pernicious anemia a macrocytic anemia with a *megaloblastic bone marrow* is seen in the anemias associated with sprue nutritional macrocytic anemia the pernicious anemia of pregnancy *the megaloblastic anemia of infancy* and the macrocytic anemia which is associated with extensive liver disease *In these conditions as in pernicious anemia when effective medication* is administered such as vitamin B 12 or folic acid within 24 to 48 hours *there begins a conversion of the megaloblastic to a normoblastic* marrow and within a few days this is complete

The Sternal Marrow in Chronic Hemolytic Anemia —*In this condition* there is extreme activity of the bone marrow as indicated by a greatly

The following are the results of average differential cell counts from the sternal marrow as reported by the mean counts of 21 different observers using various techniques as collected by Albritton (34) *Red blood cell series* 19 1 per cent early 2 9 per cent (proerythroblasts 0 5 per cent and early normoblasts 2 4 per cent) late 16 2 per cent (intermediate normoblasts, 11 7 per cent and late normoblasts, 4 5 per cent) *granulocytic* 57 4 per cent myeloblasts 1 2 per cent progranulocytes 3 0 per cent *myelocytes* 8 7 per cent *metamyelocytes*, 11 0 per cent band cells 17 9 per cent segmented cells 15 6 per cent *others* 12 6 per cent lymphocytes 9 8 per cent, monocytes 1 4 per cent megakaryocytes 0 2 per cent plasmocytes 0 6 per cent reticulum cells 0 6 per cent, *not identifiable* 10 9 per cent unclassified 1 7 per cent disintegrated cells 9 2 per cent

The Sternal Marrow in Patients with Acute and Chronic Hemorrhage —Following the sudden loss of a significant quantity of blood both the erythroblastic and myeloid elements of the sternal marrow show hyperplasia especially the former There is an increase in the number of normoblasts and the reticulocytes Mitotic figures are observed to be more frequent than normal but such changes occur at the normal level of cell development Megakaryocytes are increased in numbers

In chronic hemorrhage with a resultant iron deficiency there is an increase in active erythropoiesis The degree of this change is dependent upon the severity and duration of the anemia In some instances there is a moderate increase in the cellularity of the marrow There may be many mitotic figures of the normal type present The number of reticulocytes is fairly large but not so great as following the acute loss of blood

The myelocytes are approximately normal in number There is no increase in the number of normoblasts following iron therapy which is interpreted to mean that iron is necessary for the completion of the final stage of erythropoiesis but not as a stimulus to the formation of normoblasts It is stated by some (35) that if the anemia has been present for a long period of time the bone marrow may become hypoplastic or aplastic but I have not observed this in patients with this type of anemia of long duration

Pernicious Anemia in Relapse —The cellularity of the marrow in this condition is increased and the relatively great number of megaloblasts present in the material is striking The megaloblasts and promegaloblasts may make up as many as 45 to 65 per cent of all of the nucleated cells which are present There may also be an increase but to a lesser extent of the normoblasts although this is a less distinctive alteration The megaloblastosis is interpreted as due to a maturation arrest at the megaloblast stage Also increased are the hemocytoblasts which are cells with a basophilic cytoplasm devoid of granules and with a nucleus which is denser than that of the hemohistioblast although it has the same reticular structure This cell is regarded by some as the most primitive stem

locytes and the platelets of the circulating blood In the histologic examination of the marrow from such a patient it is possible to find a few myelocytes occasionally but in general it may be said that the white blood cells found between the fat cells of the marrow are plasma cells lymphocytes monocytes or primitive histiocytes

If the marrow is examined histologically and many sections reviewed it may be possible in some instances to find islands of relatively normal bone marrow This may account for some of the puzzling findings in the peripheral blood such as a slight increase in reticulocytes or an occasional nucleated red blood cell Furthermore it should be kept in mind that when patients with the peripheral blood picture of aplastic anemia namely a reduction in the erythrocytes thrombocytes and granulocytes have a hyperplastic marrow the syndrome of "hypersplenism should be given careful consideration as a basis for the hematologic picture *The fact that the peripheral blood may show the changes of aplastic anemia in association with a normal or even hyperplastic bone marrow* has been emphasized by Thompson Richter and Edsall (36) It has been suggested by Jaffé (37) that such cases should be designated as pseudoaplastic anemia

It is recognized that there are no distinctive differences in the bone marrow in the idiopathic and the secondary types In osteosclerotic anemia the bone marrow changes into connective tissue which later becomes ossified Occasionally the marrow cavity may undergo obliteration with bone thereby making it impossible to obtain samples of active marrow This may occur in senile osteosclerotic anemia or in Albers Schonberg s marble bone disease

The Bone Marrow in Leukemia—Chronic Myelogenous Leukemia — In this condition the diagnosis is usually apparent from the physical examination and the findings in the peripheral blood In patients with subleukemic leukemia however in which the white blood cell count is below or within normal limits and there are only a few abnormal white blood cells present the findings in the bone marrow may be of the greatest diagnostic importance

The characteristic changes in the marrow of a patient with chronic myelogenous leukemia are (1) the presence of an increased number of myeloblasts often exceeding greatly the normal number of 1 to 2 per cent (2) *the striking increase in the number of myelocytes* of which a very large percentage are neutrophils although large numbers of basophils and eosinophils are also present (3) when the leukemic process is fully developed there is a definite increase in the cellularity of the marrow there being 75 to 85 cells per high power field and (4) mitotic figures are not numerous but it is often possible to find them usually in myelocytes or sometimes in myeloblasts after a careful search

Some evidence bearing on the acuteness of the process may be obtained by an estimation of the relative number of myeloblasts and other

increased cellularity. In other words a pronounced hyperplasia is present. About 75 per cent of the marrow cells are nucleated red blood cells at the normoblast stage although a few are as young as the proerythroblasts. Although it has been claimed by some (35) that true megaloblasts may be present in cases of Bartonella infection with a severe and prolonged hemolytic anemia it is exceedingly rare to observe this primitive stage of the red blood cell in any of the hemolytic anemias. The variety of red blood cell found in this type of marrow varies from the mature normoblast to the younger cell of this series with a basophilic cytoplasm which constitute the majority of the cells present. Reticulocytes are observed in greatly increased numbers. Granulopoiesis is normal.

The macrocytic anemia which may be present in some of the hemolytic anemias is attributed by Piney and Hamilton Paterson (35) to the fact that the nucleus is extruded early in the normoblastic cycle. There does not appear to be any correlation between the changes in the bone marrow and the level of the red blood cells and hemoglobin in the peripheral blood. This perhaps is because the production of red blood cells is probably constantly proceeding at an excessive rate which means that the marrow will be found at each examination to be hyperplastic. The level *of the red blood cell count, on the other hand may be more closely cor* related with the rate of red blood cell destruction. These two factors which operate independently could account for the discrepancies between the findings in the bone marrow and peripheral blood.

Sternal Marrow in Sickle Cell Anemia.—The bone marrow changes in this condition are similar to those found in any type of hemolytic anemia, namely the occurrence of a large number of nucleated red blood cells. Usually they average between 50 and 75 per cent of all the cells in the marrow. The predominating variety is the normoblast. Megaloblasts are not present. The only difference between the bone marrow in this type of hemolytic anemia and other varieties is the presence of sickle cells.

The Sternal Marrow in Erythroblastic Anemia (Mediterranean Anemia, Cooley's Anemia).—The bone marrow in this condition resembles that of patients with hemolytic anemia. Nucleated red blood cells, myelocytes and megakaryocytes are numerous. Phagocytes are present and may contain iron pigment. Foam cells are said to be present in small islands.

The Sternal Marrow in Patients with Aplastic Anemia.—In true aplastic anemia the bone marrow fails in its functions of producing red blood cells, granulocytes and megakaryocytes and is found to be hypoplastic in nature. Aplasia of the red blood cell forming elements alone rarely if ever occurs. In patients with aplastic anemia it is to be expected that sternal puncture will reveal a striking reduction in all of the cellular elements which accounts for the diminution in the red blood cells, the granu

often retarded as evidenced by a reduction in all types of normoblasts especially the more basophilic forms

In the *Naegeli type of monomyelocytic leukemia* the marrow in general may be said to resemble more closely that of chronic myelogenous leukemia but in which there occurs a certain number of monocytes promonocytes and monoblasts The same picture therefore, occurs in the marrow as in the peripheral blood

Bone Marrow Changes in Acute Leukemia—This condition may be either an acute exacerbation of a chronic type of leukemia or a primary state Regardless of the variety the changes in the blood and bone marrow are the same The bone marrow is found to be infiltrated with large numbers of cells of the white blood cell series which are in a primitive state of development It is exceedingly difficult as it is in the peripheral blood to differentiate positively between myeloblasts lymphoblasts and monoblasts Hence from the standpoint of the bone marrow if one observes that there is a heavy infiltration with cells of the primitive white cell variety it can be said that an acute leukemia is present but there is usually difficulty in differentiating the type The three characteristics of an acute leukemia in the bone marrow are 1 the marrow is filled with immature non granular cells 2 the nuclei of which contain nucleoli and 3 mitotic figures are numerous

Sternal Puncture in Multiple Myeloma—There is no question but what sternal puncture in patients with multiple myeloma yields valuable information which is either diagnostic or at least confirms the clinical impression that the patient has the disease Every patient with multiple myeloma whom we have seen has had the characteristic changes in the sternal marrow with one exception Normally there is about 1 per cent or less of plasma cells in the sternal marrow whereas in patients with multiple myeloma these cells or very similar ones are found to be increased usually from 10 to 20 per cent In some instances they may reach a percentage of 50 or more

The so-called multiple myeloma cell which is either a plasma cell or one closely related to it measures from 15 to 30 microns and contains a nucleus which is commonly eccentrically placed It stains deeply but the cart wheel arrangement of the chromatin is uncommon The cytoplasm is basophilic and there is a pale perinuclear zone present in some cells but not all Studies with staining methods specific for the plasma cell such as Pappenheim's pyronin methyl green have been said to give unequivocal results (25)

A study has been made by Diggs and Sturdge (39) of the peripheral blood and sternal marrow of 55 patients with plasma cell myeloma These observers report a cellularity greater than normal in all cases with an increase in plasma cells which varied from 4 to 90 per cent The number of plasma cells was more than 10 per cent in 48 of the 55 cases Fur

cells of the granulocyte series which are less differentiated than the myelocytes When the myeloblasts attain a percentage of 40 or 50 it is likely that the leukemic process is acute

According to Piney and Hamilton Paterson (35) another distinctive change is the presence of islets made up of premyelocytes and myeloblasts which indicates that the immature marrow cells in leukemia have a more focal arrangement than normal According to these observers it is in these islets that mitotic figures are most commonly seen

The Changes in Chronic Lymphatic Leukemia —As long ago as 1904 Banti (38) described four progressive changes which occurred in the bone marrow of patients with this condition They were (1) hyperemia (2) simple hyperplasia of the elements normally present (3) focal collection of lymphocytes and (4) a diffuse lymphocytic metaplasia In his opinion the longer the duration of the disease the more advanced were these changes

The outstanding feature of the sternal marrow obtained by diagnostic puncture in this form of leukemia is the great predominance of lymphocytes It is estimated that usually these cells make up from 40 to 95 per cent of all nucleated cells in the marrow in both the leukemic and subleukemic cases According to Scott (25) the findings of over 40 per cent of lymphocytes in the marrow suffices for a positive diagnosis but a normal count does not exclude the condition In my opinion however it would be more accurate to state that a percentage of over 40 per cent of lymphocytes suggests the diagnosis of lymphatic leukemia but such a finding should not be interpreted to mean that it is incontrovertible evidence of the disease

In a high percentage of cases of chronic lymphatic leukemia almost all of the lymphocytes in the marrow are of the characteristic small variety In some instances however they may be of the larger immature types but rarely are true lymphoblasts seen in this stage of the disease

The examination of the bone marrow is especially valuable from a diagnostic standpoint in cases of lymphatic leukemia in the subleukemic stage In this phase the marrow is just as characteristic as when the lymphocytes are greatly increased in the peripheral blood One is unable to state from the examination of the marrow alone whether the circulating blood shows characteristic leukemic changes or not

Chronic Monocytic Leukemia—(Schilling Type) —In this condition the bone marrow shows characteristic changes which consist of a great increase in the cellularity due to excessive numbers of cells of the monocyte series In the average case from 65 to 90 per cent of all the nucleated cells of the marrow are monocytes promonocytes or monoblasts Often the number of mitotic figures is striking and they may even be seen occasionally in the immature monocytes of the blood Erythropoiesis is

in 1940 (*41*) The clinical picture resembles that of chronic myelogenous leukemia except that the roentgen ray does not have a favorable therapeutic effect and the length of life is longer after the onset of symptoms the average duration in Jackson s cases being almost 11 years The hematological picture is similar to that of myelogenous leukemia but it may simulate chronic hemolytic jaundice The bone marrow may appear normal aplastic hyperplastic or fibrotic but it never resembles the picture of leukemia The diagnosis of myeloid metaplasia of the spleen can be made during life by detecting the myeloid cells in splenic puncture along with evidence obtained by sternal puncture that the bone marrow has not undergone leukemic changes

Changes in the Bone Marrow in Infections and Leukemoid Reactions — Our knowledge concerning the changes in the bone marrow in different types of infections is incomplete and requires further study In addition to other reasons it is important to be able to recognize the picture of infection in the marrow in order to differentiate it from the changes of leukemia Such alterations have been studied by Schilling (*42*) by Barta (*43*) and by others In these publications it is emphasized that there is a progressive "shift to the left in the granulocytes depending on the severity of the infection Barta (*43*) has divided the bone marrow into four types of reaction which occur in different infections They are as follows

1 Moderate reaction with an abundance of cells
2 Intense reaction with immature cells including many myelocytes
3 Extreme reaction with many premyelocytes or even myeloblasts
4 Failure of reaction with decrease of granular leukocytes

In infections with a leukopenia such as those due to influenza and typhoid fever the findings have been reported as those of a marrow somewhat poor in cells of the granulocyte series especially those which are mature These findings have been interpreted as a "maturation arrest"

It is important to recognize the changes which may occur in patients with *infectious mononucleosis* as the clinical manifestations of this condition may be confused with leukemia The bone marrow in the former disorder is characterized as one which is slightly hypoplastic and hence has no real resemblance to the marrow of patients with leukemia There is no radical change in the marrow picture The outstanding feature is the presence of atypical lymphocytes in every field but they exhibit various changes which are not present in similar cells of the peripheral blood These are variations in the cytoplasm from a conspicuous basophilic type to one which takes little if any of the stain The nuclei also show atypical changes which vary from those showing many nucleoli to those with striking and bizarre convolutions

It should be emphasized that the alterations stated above do not always occur in patients with infectious mononucleosis as cases have been

thermore, the cells were clumped and there was an increased number of plasmoblasts and plasma cells showing mitosis Nuclear abnormalities were observed, such as multiple nuclei, nuclear fragments, and indented and lobulated nuclei There were also cytoplasmic abnormalities present in the plasma cells as follows displacement or absence of relatively unstained areas in some of the cells variation in size with a tendency toward large forms, and marked irregularities in shape Plasma cells with eosinophilic globules (Russell bodies) were observed in several cases but were not seen in a majority Observations on the blood of these patients were of interest They were as follows in counting 1000 cells no plasma cells were found in the peripheral blood in 26 of 53 cases less than 1 per cent were seen in 19, 1 to 3 per cent in four, and more than 4 per cent in four These authors believe that their observations lend support to those which have been proposed by others namely (1) plasma cells arise from reticulum cells (2) plasma cells are a distinct strain of cells morphologically different from myeloid lymphoid and erythroid types and (3) there is no sharp line of demarcation between solitary plasmocytoma plasma cell myeloma (multiple plasmacytoma) and plasma cell leukemia

In an extensive study with a bibliography of 151 articles Bayrd (*40*) concludes that plasma cells average about 1 per cent in normal bone marrow In patients with multiple myeloma these cells make up between 2 6 and 96 per cent of all leukocytic elements present There may be an increased number of plasma cells in the blood and bone marrow in other disease states such as chronic infections granulomas measles Boeck s sarcoid cirrhosis lymphogranuloma inguinale monocytic leukemia, periarteritis nodosa and possibly others Usually the other clinical manifestations of these diseases leave little doubt as to the diagnosis and hence confusion does not arise when plasma cells are increased in these conditions This author concludes further that these cells found in the bone marrow in multiple myeloma resemble plasma cells and vary from the anaplastic and immature cell to the well differentiated and almost characteristic plasma cell In his opinion when the cells displayed a pronounced degree of pleomorphism often associated with frequent mitoses and notable immaturity the prognosis was the poorest

It may be concluded from our own experience and that of others that sternal puncture affords a highly satisfactory method for the rapid and accurate diagnosis of multiple myeloma and in some cases permits the recognition of the disease when all other means fail It should certainly be applied in all cases in which there is the slightest possibility that the disease may be present If there is no evidence of multiple myeloma cells in the material obtained from sternal puncture then considerable doubt is cast upon the diagnosis although of course this does exclude the disease

Sternal Puncture in Agnogenic Myeloid Metaplasia of the Spleen — This condition was described by Henry Jackson Jr, and his associates

at the myelocyte, promyelocyte, or leukoblastic stage, the outlook is more promising.

The Sternal Marrow in Gaucher's Disease.—The occurrence of a leukopenia, thrombocytopenia, and anemia in this disease is explained on the basis that there is an infiltration of the bone marrow and replacement of the normal components with Gaucher cells. On histological examination the bone marrow is found to be extensively infiltrated with typical cells of this type. These are described as large cells varying from 20 to 40 microns in diameter, which are pale, round, oval, or polygonal in shape. They contain one or two oval or round nuclei which are relatively small and have a finely granular chromatin structure. The nuclei are usually eccentrically located near the periphery of the cell. It has been noted that in some instances the cell may become very large, measuring from 70 to 80 microns and containing 10 to 12 nuclei.

These cells should be differentiated from the foamy, wrinkled lipid cells of xanthomatosis as well as the Niemann-Pick cells. As Thannhauser says (*50*): "Gaucher cells do not stain with fat stains like Sudan III and Scarlet R or with the Smith-Dietrich stain. The Niemann-Pick cells, on the other hand, turn dark blue. Mallory stain, however, colors Gaucher cells strongly blue, while Niemann-Pick cells stain only bluish gray. It is important to note that, in contrast to xanthomatous tissue and to Niemann-Pick cells, hemosiderin can always be demonstrated in slides in organs of Gaucher's disease.... Bone marrow biopsy or sternal puncture should reveal the nature of the changes which have occurred in the bone marrow and by such means the specific nature of the cells may be determined."

Sternal Puncture in Metastatic Lesions of Bone.—In a certain proportion of cases, an experienced observer may detect malignant cells in material aspirated from the sternal marrow in patients who have carcinoma and generalized bony metastases. It is reported by Rohr and Hegglin (*51*) that in 74 cases of carcinoma it was possible to find malignant cells in the material from sternal puncture in 10; in bronchial carcinoma they described a small cell type, and in prostatic and gastric carcinoma a large cell malignant variety. Vogel, Erf, and Rosenthal (*49*) state that in a study of 12 cases of carcinoma involving different organs of the body, carcinoma cells were found in the sternal marrow of two cases of breast carcinoma with metastases to bone.... A "shift to the right" in the myeloid elements was also observed.... In eight cases of sarcoma the marrow findings were essentially normal; no sarcoma or lymphoblastoma cells were observed.

According to Piney and Hamilton Paterson (*35*), "one is surprised at the frequency with which tumor cells are found in sternal marrow in the absence of clinical and radiographic signs of metastasis." They suggest that the routine use of this procedure might disclose many cases which

reported in which the bone marrow was said to be entirely normal Doubtless the marrow alterations are dependent to some extent on the stage of the disease in which it is investigated In this respect it resembles the blood for it is well known that in the first week of the disease the peripheral blood may not show distinctive changes Furthermore it should be kept in mind that certain changes such as the occurrence of atypical lymphocytes in the material obtained from sternal puncture may be present as a result of dilution with the peripheral blood containing a large proportion of abnormal cells Although a normal marrow may occur in patients with leukemia especially lymphatic leukemia and hence such a finding does not rule out such an abnormal state it is of course imperative to differentiate the positive findings in the marrow of a true leukemia from infectious mononucleosis

Sternal Marrow in Patients with Agranulocytosis —In patients with idiopathic agranulocytosis of Schultz there may be an apparent discrepancy between the findings in the bone marrow and those in the blood In the bone marrow there is often an increased number of young granulocytes or in other words what appears to be a hyperplastic marrow whereas in the blood there is a greatly reduced number or complete absence of the granulocytes In the first reports of the bone marrow in this condition Schultz (*44*) and others who followed him stated that the bone marrow in such a condition showed aplasia and this is probably true in some instances The characteristic change however as first indicated by Fitz Hugh and Krumbhaar (*45*) is a delayed maturation of the granulocytes Subsequent studies by Fitz Hugh and Comroe (*46*) Custer (*47*) and Darling Parker and Jackson (*48*) revealed evidence in support of this observation It was Custer in 1935 who suggested that the failure of the myeloblasts to proliferate might be due to the lack of some factor which controlled the maturation of these cells It is the impression of Jaffe that the early cell forms of the granulocyte series proliferate but fail to mature because they degenerate (*37*) It is important to note that the other elements in the bone marrow do not seem to be affected Erythropoiesis and megakaryopoiesis are not changed from normal

All are not in accord with the statement that a myeloplastic or promyelocytic marrow is a common finding in agranulocytosis This is evidenced by the statement of Vogel Erf and Rosenthal (*49*) who say in regard to patients with agranulocytosis It appear that a myeloblastic or promyelocytic bone marrow during life is not a common finding In fact such a marrow is highly suggestive of leukopenic myeloid leukemia

In my experience the bone marrow in some cases of agranulocytosis shows evidences of maturation arrest at the myeloid stage and in other cases an aplasia In those cases with complete aplasia the prognosis is poor whereas if the bone marrow is hyperplastic with a maturation arrest

suggests that the blood stream may be invaded earlier than is usually believed. With hormonal therapy the tumor regresses and the anemia and tumor tissue demonstrated in the bone marrow decrease.

It should be concluded that sternal puncture may be of assistance in the diagnosis of malignancy in certain cases. This is especially true (1) when the marrow is obtained from patients with cancer which commonly metastasizes to bone, such as those with the primary growth arising in the prostate, kidney, lung and breast, (2) especially when particles of sternal marrow are examined in sections by histologic technic, and (3) when the examinations are made by experienced observers. Study of the marrow obtained by sternal aspiration by an expert is necessary to identify positively cancer cells in such material. While carefully determined positive results are of great importance from a clinical standpoint, the absence of cancer cells in a small sample of marrow is not conclusive evidence that the marrow is free from metastases elsewhere.

Sternal Puncture in Thrombocytopenic Purpura.—In general it may be stated that in this type of purpura the bone marrow does not show striking changes. In instances where the diminution in the blood platelets has resulted in prolonged hemorrhage, the marrow will show only the alterations commonly associated with this condition.

One important point should be emphasized, however, and that is the findings in the sternal marrow in relation to the possibility of splenectomy alleviating the disease. *It is known that in idiopathic thrombocytopenic purpura in which splenectomy is usually successful in relieving the condition, the bone marrow does contain megakaryocytes.* On the other hand, in the secondary varieties of the disease, such as that associated with aplastic anemia, the megakaryocytes may be greatly diminished or absent from the marrow. From my experience it is not wise to advise splenectomy in patients with thrombocytopenic purpura unless megakaryocytes can be demonstrated in the bone marrow.

Various methods of estimating the number of megakaryocytes have been evaluated and the literature reviewed by Pizzolato (58) and by Berman, Axelrod and Kumke (59).

The Sternal Marrow in Polycythemia Vera.—It is not difficult to understand why there might be some differences of opinion concerning the bone marrow finding in patients with polycythemia. In the first place there are different types of the disease, such as the secondary varieties due to recognizable causes and the idiopathic variety or polycythemia vera. These have in common only the fact that the red blood cell count is increased. Another feature which may confuse the findings in the sternal marrow in these conditions is the fact that in the true polycythemia there may be an alteration into a clinical and hematological picture which not infrequently simulates leukemia closely. As is to be expected, this finding in the peripheral blood is associated with alterations in the leukopoietic tissue in the marrow.

were thought to be operable but which had already passed through the stage in which cure is possible In their opinion probably the commonest *metastatic growths of the bone marrow* are secondary deposits arising from carcinoma of the prostate breast stomach, kidney or thyroid In addition to the presence of carcinoma cells these authors state that the marrow shows hyperplasia of the erythroblastic tissue with hemoglobinization taking place in the earlier forms of normoblasts Also areas of proliferating myeloblasts and myelocytes may be encountered, which give the general picture of a leukoerythroblastosis

In a study of 32 patients with metastatic carcinoma it was concluded by Lanier (52) that a definite deviation from the normal pattern of cell characteristics and distribution occurred in 87 5 per cent (28 patients) While actual tumor cells were identified in only 25 per cent of the patients other abnormal findings were present In the opinion of this observer an increase in the number of plasma cells reticuloendothelial cells and/or eosinophilic elements should suggest the presence of metastases

It is the opinion of Weisenberger and Heinle (53) that the diagnosis of metastatic carcinoma can be made occasionally by finding tumor cells in the sternal marrow aspirate but that frequently many bizarre atypical and distorted cells may be present and these may be mistaken for tumor cells They conclude therefore that the diagnosis of carcinoma on this basis may be open to question It is their opinion that a more accurate diagnosis is possible by finding nests of cancer cells in histologic sections made from sternal marrow particles according to a technic previously described (54 55) Using this histologic technic Weisenberger and Heinle (53) found that in 50 patients with carcinoma of the prostate 7 had evidence thus obtained of carcinoma in the sternal marrow In this group however patients were selected in whom metastatic lesions were otherwise demonstrable especially to bone They emphasize that tumor cells are much more likely to be found in the sternal marrow in patients with malignant lesions which commonly metastasize to bone namely carcinoma of the breast lung kidney and prostate If more patients with early carcinoma or with carcinomas which do not characteristically metastasize to bone were studied the incidence of marrow metastasis would be lower

A study of metastases in bone marrow of patients with carcinoma of the prostate has been made by Rundles and Jonsson (56) who state that material secured by needle aspiration and in some cases by trephine from the sternal or iliac crest showed tumor cells in 17 of the 30 patients examined Twenty one of these patients had roentgen ray or pathologic evidence of metastases In an article Alvea and Rundles conclude (57) that a study of the bone marrow aspirated from the sternal marrow cavity in patients with carcinoma of the prostate is of value because the presence of metastases thus demonstrated before the appearance of x ray changes

suggests that the blood stream may be invaded earlier than is usually believed. With hormonal therapy the tumor regresses and the anemia and tumor tissue demonstrated in the bone marrow decrease.

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In general, it may be said that in polycythemia vera the majority of authors agree that there is a *moderate increase in the cellularity of the marrow* and that the number of erythroblasts is somewhat increased. Not only is there evidence of increased activity of the white blood cells and the red blood cells but for some unknown reason there is also characteristically an increase in the number of *megakaryocytes* commonly observed.

In the opinion of Manning (60) the diagnosis of polycythemia vera is suggested by the following pattern of changes which may occur in the sternal bone marrow: there is an increased number of nucleated red blood cells especially erythroblasts over the ratio of 20 per 100 white blood cells counted; the value of reticulocytes exceeds 2 per cent, and the myeloid-erythroid ratio is below 3:1. *When such changes are observed in patients in whom the hemoglobin of the circulating blood, the red blood cell count and the hematocrit reading are above normal and in whom causes of secondary polycythemia can be excluded, the diagnosis of polycythemia is likely.* This observer states, however, that polycythemia vera may be present in a patient with an entirely normal bone marrow. It should be kept in mind, therefore, that *in some cases the bone marrow may appear to be surprisingly normal in appearance in this disorder despite the typical changes in the peripheral blood*. This is, therefore, another example of how there may be changes in the peripheral blood with few if any alterations in the bone marrow to account for them.

The Sternal Marrow in Hodgkin's Disease.—As Hodgkin's disease and allied conditions are known to have a widespread distribution in the body outside of lymph nodes and according to Limarzi and Paul, the sternal marrow is involved in 63.7 per cent of the cases (61), these observers considered that the findings on sternal aspiration might be of value from the standpoint of diagnosis. Their studies disclosed, however, that the changes were not diagnostic unless the specific pleomorphic *lesion of the disease was observed. It is their opinion that the presence of any cell or group of cells in the marrow aspirated from the sternal cavity is not sufficient evidence on which to base a diagnosis of Hodgkin's disease.* They conclude that the *most constant findings in the bone marrow of patients with the disorder are myeloid and megakaryocytic hyperplasia.* In their studies the *Reed-Sternberg cells were not seen in sternal aspirated material nor in the histologic sections of bone marrow particles from such material.* They present evidence which has led them to believe that the *giant cells of Hodgkin's granuloma are not similar to nor related to bone marrow megakaryocytes.*

Cooper and Watkins (62) *report the results of a study to evaluate the clinical usefulness of aspiration of the sternal bone marrow as a method of obtaining material of diagnostic significance.* They conclude that the *findings were not specific or consistent and hence are not of assistance*

in the diagnosis of Hodgkin's disease With improvements in technic and in the study of patients in whom there was clinical evidence of bone involvement they believe that the results might be of greater significance In seven of 10 cases of lymphosarcoma however abnormal lymphocytic cell types, thought to be diagnostic of lymphosarcoma were encountered Although no striking abnormal changes were observed in the sternal marrow aspirated from 2 patients with follicular lymphoma it was thought as this disease was closely related to lymphosarcoma that more extensive observations may indicate a greater diagnostic value of the procedure in this condition

Sternal Puncture in Protozoal Diseases—It is pointed out by Pines and Hamilton Paterson (35) that these diseases offer a promising field for study by means of sternal puncture as many of the parasites make their home in the reticulo-endothelial system According to these authors sternal puncture affords a rapid safe method of providing material which not only contains the parasites in large numbers but also affords an opportunity of studying the mechanisms of some of the blood changes

Kala Azar—In this condition there is a lymphocytosis monocytosis a hyperplasia of the cells of the reticulo-endothelial system and the causative organism the Leishmania is present The parasites are found in the monocytes and free from cells In some respects they resemble platelets but differ from them in having a much more complicated structure

A case of kala azar is reported by Senter Sutker and Carver (63) in a veteran of the United States Army who had been in the North African Sicilian and Italian campaigns He had been treated for malaria for two years before the proper diagnosis was established They point out that the laboratory findings of hyperglobinemia plasmatocytosis of the bone marrow and excessive rouleaux formation considered to be characteristic of plasmocytic myeloma are found consistently in kala azar The diagnosis may be made by the demonstration of the organisms in the bone marrow or lymph node by smear culture or hamster innoculation

Malaria—The marrow in malarial infections is hyperplastic of the normoblastic variety and resembles that seen in other hemolytic anemias According to Pines and Hamilton Paterson (35) in malignant tertian malaria the cycle occurs in the tissues rather than the peripheral blood Hence in this variety the number of infected corpuscles may be greater in the marrow than in the blood stream These authors also report that the marrow response which does not disappear for months after recovery from the acute phase of the disease is essentially normocytic and monocytic

Sternal Marrow in Miscellaneous Conditions—A study of the bone marrow *in patients with hyperthyroidism and hypothyroidism* with an extensive bibliography has been published by Axelrod and Berman (64) They report that the sternal marrow in patients with hyperthyroidism is

hyperplastic and there is an increase in red marrow in all long bones. The generalized hyperplasia of lymphoid tissue observed in patients with hyperthyroidism also involves the bone marrow. There is an increase in the megakaryocytes of the marrow but no changes in the number of circulating blood platelets. In hypothyroidism they report that there is hypoplasia of all myeloid systems. They believe that hypothyroidism should be considered in any patient having a hypocellular marrow and a *macrocytic anemia*.

A case of *Boeck's sarcoidosis* in which the diagnosis was established by the examination of material from lymph nodes and *sternal biopsy* is reported by Kennedy (65). The literature dealing with changes observed in the bone marrow in this condition is reviewed and it is stated that others have reported positive results from sternal marrow examination (*66, 67*).

According to Limarzi and Paul (*61*) sternal puncture is also of value in the diagnosis of other conditions such as *neuroblastoma* and *histoplasmosis*.

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CHAPTER XXIII

BLOOD TRANSFUSION AND BLOOD SUBSTITUTES

Introduction — The injection of human blood from one patient to another is a form of rational replacement therapy and one of demonstrated usefulness. It should be remembered however that when blood is removed from a donor and before it is injected into the veins of the recipient changes of considerable magnitude may occur which might possibly vitiate to a certain extent the effectiveness of this form of therapy. Such alterations however were more likely to occur before the modern technic of blood transfusion was perfected. It seems reasonable to assume that when whole blood is employed by the artery to vein anastomosis which is now rarely if ever used that little or no change in the transfused blood occurs. This is also likely in direct transfusions which are accomplished by the multiple syringe method and various other mechanisms which permit the rapid transfer of whole unmodified blood from the donor to the recipient.

With the advent of the citrate method in 1915 which has made blood transfusions a widely employed form of therapy the question immediately arose concerning the effectiveness of such a transfusion as compared with the so called direct methods and claims were made for or against the various technics employed in giving transfusions. In more recent years considerable discussion has arisen concerning the possible changes which may occur in blood stored in a blood bank for a period of several days to several weeks. And finally there has been a good deal of investigation regarding the usefulness of the various types of blood substitutes which have been introduced more recently into clinical medicine. Many of these questions are unanswered but there is an increasing amount of reliable information available at present which is helpful as a guide to the use of the various preparations which are now suggested as suitable for intravenous use. A discussion of the many different types of modified blood and blood which are now in use is given on page 1147.

History — The history of the development of our knowledge of blood transfusions is fascinating from many standpoints as it involves almost every phase of medicine and is fraught with national and personal controversies relating to claims of priority and jealousies which arise so often in almost every field of human endeavor. For convenience the history of blood transfusions may be divided into four periods as follows:

First Period — From the time of ancient Greek and Egyptian civiliza

tion to 1616 when William Harvey discovered that the blood circulates

Second Period —The interval between the years 1656 and 1670 which was an extremely interesting and productive one from the standpoint of blood transfusion It was at this time that the brilliant group of scientists founded the Royal Society of England and blood transfusions formed one of their earliest topics for discussion The transactions of the Royal Society *for this period contain many important references to the* subject which were contributed by Christopher Wren Richard Lower Robert Boyle, and others Also at this time, the redoubtable Frenchman Jean Baptiste Denys reported his remarkable studies

Third Period (1818) —This is concerned primarily with the investigations of James Blundell of London who was the *first to administer human blood intravenously to man*

Fourth Period —The modern era dating from the epoch making studies of Karl Landsteiner and his pupils which led to the identification of the four main types of human blood in 1901 and 1902

In the earliest period there were no important contributions to our knowledge of blood transfusions although consideration was given to the possibility that they were feasible and desirable under certain circumstances There are two references to the subject in this period which are worthy of discussion The first is the oft quoted claim that a blood transfusion was given to Pope Innocente VIII in his last illness A description of this alleged episode as given by Professor Pasquale Villari in the *Life and Times of Savonarola* (*1*) the religious reformer who lived from 1452 to 1498 sounds very realistic That an actual transfusion was attempted is seriously questioned by Rev Arnold H Mathews who writes in his *Life and Times of Rodrigo Borgia* (2) that probably the Pope was given blood to drink rather than receiving it by injection into a vein It is emphasized by this author that the saving virtue of drinking human blood was not a new idea at that time

The other incident of this early period which deserves mention is the remarkable statement of the chemist Libavius (3) of Halle in 1615 regarding a projected transfusion His description rings true in fact so true as to make one suspicion of its authenticity A careful consideration of the evidence leads one to conclude that it was based solely on the play of a highly imaginative mind anticipating that such a useful procedure *might* be accomplished in the future It is barely possible that Libavius in 1615 could have learned of the preliminary studies of William Harvey which led to his discovery of the circulation of the blood and that this served as a stimulus to his hypothetical transfusion for it is known that Harvey returned from Padua in 1602

The second period relating to the development of our knowledge of blood transfusion was brief as it lasted only from 1656 to 1670 but it was a fruitful one This is because several exceedingly important events

occurred at this time The first one evolutionary in scope was the discovery of the circulation of the blood by William Harvey, initially announced by him on April 17 1616 within a week of Shakespeare s death but not published until 1628 The second important event was the experiments of Christopher Wren the famous architect who states in a letter (4) written in the year 1656 that he had "injected wine and beer into the mass of blood in a living dog by a vein in good quantities till I made him extremely drunk This experiment Lower readily concedes, led him to his successful attempt of transfusing blood from one dog to another This classical and highly important experiment was performed about the end of February in the year 1665 at Oxford England A letter written by Lower at the suggestion of the renowned scientist Robert Boyle describing this experiment appears in the *Transactions of the Royal Society* for December 17 1666 page 353 and is also given in Lower s book on page 160 (5) It is known that Lower also transfused a human being with lamb s blood for on November 23 1667 at Arundel House twenty two months after the successful dog experiment assisted by Dr Edmund King he injected 9 or 10 ounces of lamb s blood into the vein of one Arthur Coga

In the past sufficient importance has not been given to the work of Johann Sigismund Elsholtz (1623–1688) In his book *Clysmatica Nova* first published in 1665 he discusses important experiments on the intravenous injection in animals and man and considers quite thoroughly the problems associated with blood transfusions although he did not actually perform one A translation of his work is given in *California and Western Medicine* for the year 1933 (6)

It must be admitted however after a careful consideration of all evidence that Lower was not the first to administer a blood transfusion to man There is convincing proof that Jean Baptiste Denys of Montpellier France Doctor of Physics Professor of Philosophy and Mathematics and Physician to Louis XIV reported similar observations which were undoubtedly performed at least six months prior to those of Lower The experiments of Denys are recorded in the *Philosophical Transactions* for July 22 1667 which preceded those of Lower by several months Denys transfused two persons with lamb s blood intravenously Apparently one suffered no ill effects but the other had untoward symptoms which are the earliest record of the effects of an incompatible blood transfusion On the morning after the blood had been injected the patient passed a great glass full of urine of a color as black as if it had been mixed with the soot of chimneys A transfusion which he performed later terminated fatally and such procedures were frowned upon later in France and elsewhere throughout Europe

Additional early claims have been made by others that a blood transfusion had been given Among these is the statement of Folli Francesco

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said that the operation of blood transfusion had been performed six times in New York City but in no instance had it been successful It is probable that defibrinated blood had been employed William Pepper in an article dealing with pernicious anemia written in 1873 reports that he had given blood transfusions with defibrinated blood to a number of his patients with the disease but concluded that they were capable of only temporary good and commented unfavorably on the "terrible symptoms" which frequently followed transfusions

In 1821 Prevost and Dumas (9) contemporaries of Blundell introduced for the first time a method of preventing the blood from clotting namely by defibrinating it and also they studied the effect of caustic soda in inhibiting coagulation Braxton Hicks (*10*) the well known English obstetrician in 1869 also made attempts to prevent the clotting of blood when used for transfusion by employing sodium phosphate which was suggested by Dr Frederick Pavy Apparently this substance functioned perfectly and why it was so soon forgotten is not known

It was not until 45 years later in 1914 that Albert Hustin (*11*) of the University of Brussels revived this exceedingly important step in the technic and first introduced the method which is now in universal use Shortly after this in January 1915 Professor L Agote (*12*) of Buenos Aires published a paper in which he also recorded having given a citrated blood transfusion on November 14 1914 Also in January 1915 the observations of Richard Lewisohn (13) of New York appeared in the *Medical Record* in which he reported using citrated blood in two patients successfully The work of Richard Weil (*14*) of New York City dealing with the use of sodium citrate as an anticoagulant appeared in the January 30 1915 number of the *Journal of the American Medical Association* Thus over a short period of nine months during 1914 and the early part of 1915 no less than four separate investigators reported independently on the citrate method of blood transfusion for which the whole medical world had been waiting for so many years

An important review dealing with the development of our knowledge of technic of blood transfusions since 1907 is given by Richard Lewisohn (*15*) with special reference to contributions by the members of the staff of the Mount Sinai Hospital of New York City This article is exceedingly valuable for it gives Lewisohn's personal reminiscences concerning the development of the modern method of blood transfusion in which he played such an important role He states that he started his work with anticoagulants by employing hirudin which he soon found was too toxic to use in human blood transfusions His early work done in 1915 is outstanding for the following two contributions (1) he determined that 0 2 per cent is the amount of sodium citrate required in blood to prevent coagulation and (2) 5 grams of sodium citrate can be introduced safely into the circulating blood of an adult. In regard

(7) that he was the originator of the procedure having based the idea on reading William Harvey's treatise dealing with the circulation of the blood in 1652 There is no actual proof however that he actually performed a transfusion In fact he confesses after picturing the apparatus and describing the method of administering blood, that he had not made the experiment

After an interval of about 150 years in which no substantial progress was made in perfecting this valuable therapeutic procedure James Blundell (8) of London a physiologist and obstetrician performed the first blood transfusion in which blood from one human being was injected into another On September 26 1818 an historic date of great moment from this standpoint he injected from 12 to 14 ounces of human blood into the veins of a patient by the name of Brazier who was apparently suffering from cancer of the stomach The members of the patient's family served as donors and the blood was given unchanged This was accomplished by means of a crude apparatus which permitted the blood to escape from the vein of the donor into a funnel and then enter the veins of the recipient by gravity In my own copy of James Blundell's book inscribed by him (8) a full account of his experiments on blood transfusions is given There are many notes in Blundell's handwriting on the margins of the pages which was Blundell's own personal copy Unfortunately from the standpoint of the history of blood transfusions the notes are concerned almost entirely with the operation of vaginal hysterectomy in a human which he accomplished successfully in 1828

The publication of Blundell's important contributions came to the attention of the medical profession in America as indicated by the appearance of a resume of his work in the first volume of the *Boston Medical and Surgical Journal* in 1828 only three years after the appearance of his book on *Researches Physiological and Pathological* The comments were written by Walter Channing the obstetrician of Boston and Dean of the Harvard Medical School from 1819 to 1847 He states that if such an experiment be tried in this country it will give the editors of this *Journal* much pleasure to communicate the results *in its* pages This implies that a blood transfusion had not been given in the United States prior to that time

The earliest reference to a blood transfusion in this country which I have been able to find is a note at the conclusion of an abstract of Blundell's work in the *Philadelphia Journal of the Medical and Physical Sciences* volume IX for the years 1825 and 1826 In this it is stated that 30 years before (*circa 1796*) a blood transfusion had been given by Philip Syng Physick who has been called the Father of American Surgery but my careful search through the literature has failed to reveal any publication confirming this

On January 15 1874 *there was a stated meeting of the New York* Academy of Medicine presided over by Austin Flint Sr in which it is

agglutinins for other red blood cells but whose red blood cells were agglutinated by all other human sera. In other words, this was what is now designated as group AB. Although this information was made available in 1901, apparently its importance was not at once appreciated, for it was not until 1908 that Ruben Ottenberg published his studies which indicated the importance of selecting donors on the basis of agglutination tests.

Lewisohn (15) in commenting on this work says "Ottenberg deserves much credit for connecting Landsteiner's work with human blood transfusions. In 1907, when still an intern at the German Hospital, now the Lenox Hill Hospital, in New York, he was the first to match donor and recipient before a blood transfusion *(18)*. Looking back, it seems incredible that six years should have elapsed before Landsteiner's work was put to practical use." The reminiscences of Ottenberg *(19)* are of unusual interest in this connection.

In 1907, Janský *(20)* labeled the four groups by the numerals I, II, III, IV and in 1910 Moss *(21)* recognized the four groups but reversed the order of the numerical designations. Although the Moss System was used widely in the United States for some years, it did cause confusion and in recent years, very properly, there has been a return to the original A, B, O nomenclature of Landsteiner.

In 1940, the Rh blood types were discovered by Landsteiner and Wiener (22), and in the same year it was emphasized by Wiener and Peters (23) that the use of an Rh positive donor could be responsible for a hemolytic reaction and even death in a recipient with an Rh negative blood.

Important contributions were made in the technic of blood transfusions in the early years of the twentieth century. In 1902, Alexis Carrel published his first study on the anastomosis of blood vessels which later led to a successful performance of blood transfusions by the method of artery to vein anastomosis. His studies were recognized by the award of the Nobel prize in 1912. In 1907, George Crile introduced his improved technic of inserting a cannula between the artery and vein. This method was a considerable advance which resulted in the performance of an increased number of blood transfusions.

It was obvious that the valuable procedure of blood transfusion, however, could never be commonly employed until more simplified methods of performing it were introduced. This is because any method of direct transfusion has several handicaps. One was that it was a considerable inconvenience to both the donor and the recipient. The other was that definite information concerning the amount of blood which had passed from the recipient into the donor's veins could not be estimated accurately. This led to the development of methods of introducing blood by various indirect procedures. Some of these were based on the observation first

to the others who almost simultaneously reported on the value of sodium citrate as an anticoagulant in blood transfusions Lewisohn has this to say 'Agote should get proper credit His paper appeared exactly the same time as my original communication (January 1915) He had the right percentage of sodium citrate (0 25 per cent) I have often said that when an idea is ripe it frequently occurs simultaneously to more than one person Thus Agote and I, in different and far distant parts of this hemisphere hit upon the right technique at the same time"

It is stated by Lewisohn (*15*) that The same cannot be said about Hustin and Weil He records that neither Agote or I knew about Hustin's publications in a Belgian medical paper as the foreign litera ture was inaccessible during the World War He objected to the recognition of Hustin s claim because "He made the error of assuming that in order to prevent coagulation he had to mix the citrated blood with equal parts of glucose solution Naturally if Hustin s con clusions had been right and if his advice had been followed citrate transfusion would never have made the grade While I do not wish to detract from the contribution of Lewisohn which was substantial I must confess that I am not in accord with his statement which minimizes the prior work of Hustin In regard to the original work of Weil it is said by Lewisohn that he used a 1 per cent mixture of sodium citrate and blood in other words the same mixture which had been the standard mixture in laboratory work Apparently Lewisohn regarded such a high percentage of citrate as dangerous and for that reason intimated that Weil should not be credited with furthering the use of citrated blood transfusions

In addition to the prevention of clotting the other major difficulty in the transfusion of blood was the serious reactions which occurred with great frequency These untoward symptoms were regarded by some as due to unrecognizable causes and were attributed by others to the accidental injection of air bubbles The real basis for almost all of the serious reactions is of course, now known to be hemolytic in nature due to the injection of incompatible blood The satisfactory solution of this problem from which the whole world has benefited immeasurably must be credited to the monumental work of Karl Landsteiner For this he was the recipient of the Nobel Prize in 1930 His original publication (*16*) was in the *Wiener klinische Wochenschrift* in 1901 In this he recognized three groups of individuals on the basis that the red blood cells of some were or were not agglutinated by the sera of others He recognized the great significance of his discovery from the standpoint of safety in giving blood transfusions His groups were A B and O Shortly after this publication in 1901 Decastello and Sturli (*17*) one of whom had been associated with him as a pupil discovered that a small percent age of persons belonged to a fourth group whose serum did not possess

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made by Bordet and Gengou in 1901 (*24*) that the coagulation process could be delayed if the blood came in contact only with surfaces which had been coated with paraffin This principle received its first trial for the transfusion of blood by Curtis and David (*25*) in 1911 The same idea was used by Kimpton and Brown (*26*) in 1913 and subsequently modified by a number of observers In 1913 Lindeman (*27*) introduced a method, the principle of which had first been utilized by Ziemssen (*28*) in 1892 It consisted of multiple large syringes with which blood was taken from the donor s veins and injected rapidly into those of the recipient s The latter technic was employed in 1916 in the first transfusion which I observed as a third year medical student This was performed by Dr Roy McClure then resident surgeon at the Johns Hopkins Hospital late Surgeon in Chief of the Henry Ford Hospital His interest in the subject had been stimulated by Dr William S Halstead who had long been concerned with methods of transfusing blood In 1915 Unger introduced a four way valve attachment in which the blood was withdrawn from the donor and injected into the recipient with great ease in the hands of an experienced operator While these improved methods were of great value they were all superseded by the almost universal use of the simplified indirect method which employed sodium citrate as an anticoagulant Time has demonstrated that this technic is superior in every way to all of the more complicated methods which do not make use of this chemical to prevent clotting

The more recent advances in this field are those relating to the use of preserved blood Following the experimental work of Rous and Turner at the Rockefeller Institute (*29*) and of Burmeister in Chicago (*30*) Oswald H Robertson (*31*) then a medical officer attached to the British Army first employed preserved blood in treatment of the wounded at the Battle of Cambrai during the spring of 1918 It was not until 1928 that the Russians Shamov (*32*) and Yudin (*33*) began their studies on cadaver blood which in 1937 stimulated an interest in the establishment of a blood bank at the Cook County Hospital and the use of preserved blood in the Spanish War with reported success

The introduction of desiccated blood serum followed the work of Elser (*34 35*) and Flosdorf and Mudd (*36*) who perfected a method whereby plasma might be desiccated at a low temperature under a partial vacuum and when thus prepared it could be preserved indefinitely without refrigeration Also in 1936 Elliott (*37*) demonstrated that plasma could be separated from the red blood cells and kept at room temperature in liquid form for intravenous use

Beginning in 1941 Edwin J Cohn and his collaborators have made many important contributions dealing with the various protein fractions of human plasma A summary of this work is given in the July 1944, issue of the *Journal of Clinical Investigation* and a later general article by Cohn is to be found in the *American Scientist* (*38*)

Among the articles published in more recent years dealing with the history of blood transfusions are those of Zimmerman (39), Hearn (40), Keynes (41), and in 1952 there appeared a comprehensive recapitulation dealing with the history of the rhesus types by Alexander Wiener (42).

The Functions and Composition of Blood.—Before considering the indications for the use of blood transfusions and blood substitutes, a few statements concerning the composition and function of blood in the human body should be considered. The main functions may be indicated briefly as follows:

1. *Respiratory.* The transport of oxygen from the lungs to the tissues and of carbon dioxide from the tissues to the lungs for excretion.
2. *Nutritive.* The distribution of food materials such as fats, carbohydrates, amino acids from the alimentary tract to the various parts of the body where they are utilized.
3. *Excretory.* The transportation of the multiple waste products of the body, such as urea, creatinine, uric acid, and so forth, to the kidneys, liver, and skin for excretion.
4. *The maintenance of the water content of the tissues.*
5. *Regulation of the body temperature.*
6. *Protective.* The blood and lymph contain white blood cells, certain chemical substances of a complex nature, antitoxins, lysins, and other antibodies which constitute the basis of the body's defense against injurious agents of various kinds.
7. *Regulatory.* The circulation of various hormones, enzymes, vitamins, and other substances through the body.
8. *The control of the pH* between 7.3 and 7.45 by the buffer systems and maintenance of the proper electrolyte concentration.

Indications for Blood Transfusions.—There are a number of rational indications for blood transfusions which are based upon the physiology of the blood, the main ones being as follows:

1. To increase the number of red blood cells and hemoglobin content of the blood in patients with anemia and thereby combat anoxemia.
2. To increase the blood volume in order to maintain the efficiency of the circulatory system.
3. To augment the protein and electrolyte content of the blood and maintain the proper osmotic pressure relations with the body tissues.
4. To correct coagulation defects by making available functionally effective prothrombin, thromboplastin, and to a lesser extent, blood platelets.
5. By the addition of immunological factors to combat infection.

It is not possible to improve on the remarkably accurate general statement concerning the indications for the use of blood transfusions made by Leisrink in 1872 (43). He says, transfusion is indicated in all those pathologic conditions where the blood, in quantity and quality, is so altered that it is unfit to fulfill its physiological duties.

In general it may be stated that the main clinical indications for the use of blood transfusions are as follows

1 In the treatment of anemia when no other form of antianemic therapy is effective

2 In order to sustain the patient until a diagnosis can be made or

3 As a preoperative or postoperative measure

4 In the treatment of acute or chronic hemorrhage

5 As a therapeutic measure in shock

6 As a means of expediting the return of the blood to normal in chronic hemorrhage when the source of the bleeding has been controlled or in conjunction with other antianemic therapy

7 As an adjunct to other forms of combating infection

8 In the treatment of hypoproteinemia

9 To control bleeding in hemophilia hypoprothrombinemia and less effectively in thrombocytopenic purpura

Sites for the Administration of Blood and Blood Substitutes —All will agree that the customary and most convenient site for the administration of blood and other fluids is a vein in the antecubital fossa In certain patients especially those who are obese and in those in shock with collapsed veins and with extensive burns these veins cannot always be used It is well to have in mind other veins which may serve the purpose very satisfactorily Rarely if ever in my opinion is it permissible to incise the skin and expose the veins because this is hardly ever necessary and the further use of such veins may be impossible It is easy in some instances to use the femoral vein which is large and usually easily located It is situated just medial to the femoral artery which is readily felt in the inguinal region According to Dameshek (*44*) administration of plasma by this route was found extremely useful by the Boston City Hospital group during the Coconut Grove fire disaster in 1942

The infusion of blood and other fluids through the sternal marrow is a very satisfactory method to employ if other routes are not accessible This method was used by Tocantins (*45*) in 1941 and has been proven by experience to be of considerable value Turkel and Bethell (*46*) have devised a special needle for this purpose which is very useful

In infants less than one year of age the scalp veins or veins of the dorsum or the hand can be utilized satisfactorily in the first few days of life the umbilical veins are also available for transfusion purposes The superior longitudinal sinus in infants is easily entered with a transfusion needle but should not be used as hematomata may be formed The bone marrow cavity of the sternum tibia and the femur may be used in children in patients under three years of age however the sternal cavity should not be employed because it is undeveloped at that stage of life Intraperitoneal blood transfusions have been given both to adults and infants (*47*) but the absorption is slow and uncertain and other hazards

make it undesirable (48) In general it should be emphasized that it is advisable to inject blood intravenously for transfusion purposes both in infants and adults rather than employing any other sites which have been discussed

Treatment of Anemia When No Other Form of Antianemic Therapy is Effective—All too often one is confronted with a patient who has an anemia for which there is no available effective therapy In some instances its cause may be recognized as a non controllable chronic hemorrhage which is inaccessible to surgery or to a chronic infection which does not respond to therapy In such conditions the rational use of blood transfusions may give symptomatic relief or sustain the patient until the primary cause of the anemia is eliminated In other types of anemia for which there is no form of effective therapy repeated blood transfusions are likewise often of value A few of the more important anemias where this is the case are aplastic anemia myelophthisic anemia such as that present in lymphoblastoma and leukemia the anemia of nephritis the anemia of malignancy Cooley s anemia sickle cell anemia and achrestic anemia In such patients the availability of the blood bank in many hospitals makes repeated blood transfusions possible The blood in such patients should be kept within approximately normal limits if this can be accomplished In any event the hemoglobin should be maintained at a level of at least 11 grams per 100 cc (70 per cent) as the symptoms attributable to an anemia are then largely controlled

Blood Transfusions in Aplastic Anemia—While this condition is not common it is probably more frequently encountered than available statistics would lead us to believe and appears to be increasing in incidence in recent years Experience to date has shown that there is no form of therapy which accounts for the slightest improvement in these patients except blood transfusions These should be employed as frequently as indicated by the presence of symptoms

The rationale for the use of blood transfusions in this condition may be stated as follows (1) They will provide the patient with sufficient red blood cells and hemoglobin to control the more distressing effects of anoxemia such as extreme weakness dyspnea and palpitation In one such patient who remained under my observation for a period of four years it was possible to maintain him in an ambulatory condition and permit him to indulge in his favorite form of diversion which was swimming This was accomplished by the administration of 131 blood transfusions Reference to this case is made under the section of aplastic anemia and along with it a warning is issued that such a large number of blood transfusions may result in hemochromatosis as it did in this patient and terminate in death Reference to 30 similar cases of transfusion siderosis has been made by Brown *et al* (49) Even though the

remedy which gave my patient comfort for four years undoubtedly contributed to his death the symptomatic relief afforded was worth while Knowing the possibilities as I do I can honestly say that under the circumstances I would insist on a sufficient number of blood transfusions if I had a similar condition to keep myself comfortable regardless of the possible dangerous and even fatal complication (2) Blood transfusions should be given in aplastic anemia also in an attempt to control the bleeding due to the associated thrombocytopenia although this often cannot be accomplished (3) It is worth while to prolong the life of a patient with aplastic anemia by means of blood transfusions because in some instances a spontaneous remission may develop which will persist for some months One of my patients a male of 24 years, had a red blood cell count below 1 0 million per cubic millimeter but fortunately developed a spontaneous remission after many blood transfusions had been given His red blood cell count returned to normal and the patient was again able to work for a period of six months during which time he remained in perfect health before a fatal relapse occurred

Blood Transfusions in the Treatment of the Anemia Associated with Chronic Glomerular Tubular Nephritis —In this condition as the disease progresses there is invariably a moderate to severe normochromic, normocytic anemia which contributes importantly to the symptomatology of the patient There is no known effective antianemic remedy available for the control of this form of anemia except the use of multiple blood transfusions In my experience the presence of such an anemia in a patient with nephritis is usually indicative of a pronounced renal insufficiency and heralds the approach of the terminal state In my hands blood transfusions have been productive of considerable symptomatic relief due to increasing the circulating hemoglobin and possibly to correcting the electrolyte deficiencies of the plasma commonly seen in this condition Other observers (*50*) have been optimistic about the results produced by transfusions

Blood Transfusions in Lymphoblastoma and Leukemia —In both of these diseases blood transfusions serve a very useful purpose This is because eventually an anemia will appear in all forms of these conditions and progress to the point where the symptoms on this basis are likely to dominate the clinical picture When the anemia first appears it is usually benefited by exposure to the roentgen rays and nitrogen mustard injections but as the disease progresses these forms of therapy become less and less effective When this stage of the disease arrives therefore considerable improvement may be derived from the use of repeated blood transfusions Furthermore when the red blood cell count is below 3 5 million per cubic millimeter and the hemoglobin less than 65 per cent (10 14 grams per 100 cc) then one or more blood transfusions should be given prior to roentgen therapy This is because not infrequently roent

gen therapy may cause an actual depression in the hemoglobin and red blood cell count which is apparent within a few weeks following the exposures. The anemia in both conditions is not benefited by the administration of iron, liver, or stomach therapy.

In leukemia, and less frequently in Hodgkin's disease, there often develops a secondary thrombocytopenic purpura which is likewise due to the infiltration of the bone marrow and a consequent reduction in the number of megakaryocytes, the precursors of the blood platelets. When this state develops, there is commonly pathological bleeding into the skin and mucous membranes and not infrequently into the various organs of the body. The only form of therapy which may be of help in this condition is repeated blood transfusions with fresh blood. The use of "bank" blood in thrombocytopenic purpura is contraindicated as the platelets are agglutinated in stored blood within a few hours after it *is drawn and therefore they probably do not function normally to* check the bleeding of this type of purpura.

***The Use of Blood Transfusions in Sickle Cell Anemia and Cooley's* (Mediterranean) Anemia.**—It is recognized that there is no form of effec*tive treatment in these types of anemia except the transfusion of blood.* Although patients with these conditions do not usually live out their normal span of life, it is not rare for them to reach middle age and sometimes survive even a greater length of time. This is especially true of patients with sickle cell anemia, and in more recent years it is appreciated that the life span of patients with Cooley's anemia is longer than had been previously supposed. In such patients, the anemia which is always present to some degree, and sometimes is advanced, is the most frequent basis for the patient's symptoms.

In both conditions, probably as the result of the long standing anemia, there is cardiac involvement with its associated symptoms. In some instances it is chronic congestive failure which is the cause of death. In one of my patients with Cooley's anemia, age 14, in whom the condition had been known to exist since the age of 2½ years, the hemoglobin usually ranged between 2.5 and 5.0 grams per 100 cc. of blood. He was not as cooperative as was to be desired in reporting for treatment and consequently lived with a severe anemia for a greater portion of ten years. All of the signs of advanced congestive failure developed, which resulted in death within a short time. It is probably true that if more blood transfusions had been given over the years, his heart would have been spared to a certain extent and his life prolonged. Hence in any type of hemolytic anemia for which there is no treatment and in which the cause cannot be removed, an effort to maintain the hemoglobin of the circulating blood in the vicinity of 11.0 grams per 100 cc., or higher if this is possible, should be made.

The Use of Blood Transfusions in Patients with Anemia Due to Malignancy.—I am a strong advocate of the use of all measures in the treatment

remedy which gave my patient comfort for four years undoubtedly contributed to his death the symptomatic relief afforded was worth while Knowing the possibilities as I do, I can honestly say that under the circumstances I would insist on a sufficient number of blood transfusions if I had a similar condition, to keep myself comfortable, regardless of the possible dangerous and even fatal complication (2) Blood transfusions should be given in aplastic anemia also in an attempt to control the bleeding due to the associated thrombocytopenia although this often cannot be accomplished (3) It is worth while to prolong the life of a patient with aplastic anemia by means of blood transfusions because in some instances a spontaneous remission may develop which will persist for some months One of my patients, a male of 24 years had a red blood cell count below 1 0 million per cubic millimeter but fortunately developed a spontaneous remission after many blood transfusions had been given His red blood cell count returned to normal and the patient was again able to work for a period of six months during which time he remained in perfect health before a fatal relapse occurred

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imminent The admission diagnosis was cancer of the stomach based on the outstanding feature of her case which in addition to shock was the vomiting of large quantities of blood It was not possible to obtain a detailed history The decision to be made was whether she had an incurable cancer of the stomach which would not respond to any form of therapy or some other condition which might be benefited by some form of antianemic medication In the absence of a definite diagnosis it was decided very properly to give the patient repeated blood transfusions to meet the immediate emergency This was done in the hope that her condition would be improved to such an extent that diagnostic studies could be made She responded satisfactorily to the transfusions and within a period of about one week was able to undergo various tests including gastro intestinal roentgen ray studies It was ultimately determined that she had cirrhosis of the liver While the prognosis with this condition is not promising it is better than that of carcinoma of the stomach as I have seen patients with cirrhosis of the liver as far advanced as it was in this patient survive for several years

Another situation which the attending physician should keep in mind concerning the treatment of patients with a severe anemia is that death may occur before the patient has time to respond to potent antianemic therapy For example in the early days of liver therapy I once saw a patient with pernicious anemia succumb because when he was admitted to the hospital in a serious condition and although the diagnosis was clear it was thought then that there was no means of administering liver except by ingesting the substance in a cooked form Although this may appear grossly negligent in the light of our present knowledge it should be remembered that this occurred in the very early days of liver therapy before it had become definitely established as a potent form of treatment Furthermore although it was recognized that the patient s condition was serious it was not anticipated that he was likely to die in such a short time This patient did not die without impressing on us the importance of being prepared for such an emergency A short time later another patient in a similar condition was admitted to the same hospital He was immediately transfused and effectively treated by giving one half pound of raw liver suspended in water by means of a stomach tube with gratifying results

It is advisable therefore when first observing a patient to evaluate carefully the condition from the standpoint of the immediate prognosis If there is the slightest risk involved which might be controlled by blood transfusions obviously they should be given immediately It is known from experience that even when highly potent liver extract or vitamin B_1 is administered in large doses parenterally the earliest beneficial effect cannot occur until after a latent period of 36 to 48 hours has transpired It has been my custom since the earliest days of liver therapy to

of the anemia of malignancy regardless of the cause. This is on the basis of my experience that the patient is made more comfortable due to the relief from extreme weakness and ease of fatigue. If pain is present it can be readily controlled by the liberal use of morphine. In some patients it is possible to benefit the anemia by the use of iron in adequate amounts or by providing a better diet. Occasionally liver extract is beneficial. If none of these measures results in improvement, then repeated blood transfusions should be given until the maximum improvement has been attained.

My experience with the benefit derived from blood transfusions in patients with cancer is well illustrated by the course of events which occurred in association with a friend of mine, a physician and medical educator. He developed a cancer of the stomach at the age of 39 years and with it a severe anemia due to acute and chronic hemorrhage from the gastro-intestinal tract. As he was thoroughly acquainted with the nature of his condition he was asked if he desired to have blood transfusions. His reply was, "Yes, give me a sufficient amount of blood to make me comfortable." This did not require many transfusions but they were responsible in part for his return to work and for giving him sufficient strength to survive for four years. During this interval he saw his sons grow up to the age when they could remember him and he was in sufficiently good health to write a number of important papers dealing with anemia.

The Use of Blood Transfusions to Sustain the Patient Until a Diagnosis Can Be Made, or Until Potent Antianemic Therapy Can Become Effective, or as an Essential Preoperative and Postoperative Procedure.—It should be impressed upon all physicians that when a patient with a severe anemia is first observed the most urgent matter to be determined is the immediate prognosis. Often it is only possible to state that the patient has an extremely severe anemia which may prove fatal within a short time unless the proper measures are immediately instituted. Under these circumstances one or more blood transfusions should be given without delay to insure the immediate safety of the patient in so far as this can be accomplished. Often it is not possible nor feasible, regardless of the urgency, to subject such patients at once to such diagnostic procedures as gastro-intestinal studies or other tests which put them under a considerable strain or require their cooperation. If life can be sustained until the patient is in such shape to undergo various diagnostic tests it may be found that the anemia is of the type which responds to various forms of antianemic therapy such as liver extract, iron, the roentgen rays, splenectomy or some other effective therapeutic measure.

A patient who was under my care illustrates to a certain extent what has just been said. She was 38 years old and was admitted to the hospital moribund and in such a precarious condition that death appeared

should become elevated to 80 per cent from this means alone in less than one week. His convalescence therefore would be materially shortened. There is no evidence that the normal activity of the bone marrow will be inhibited when this is done.

The problem might also be considered from the standpoint of pernicious anemia. If a patient with this condition had a red blood cell count of one million per cubic millimeter and was given potent antipernicious anemia therapy in adequate doses then it is known from experience that the red blood cell count would increase at the rate of approximately 400 000 erythrocytes per cubic millimeter per week. This would mean that the blood would approach normal limits in about eight weeks. On the other hand the patient would be up and about with few if any complaints long before this time even though the red blood cell count was below normal. The possibility that several blood transfusions might cause the blood to return to normal in a shorter time must be admitted. The possible depressing effect of blood transfusions however on the rate of formation of erythrocytes must be taken into account. *At present transfusions under these circumstances are not recommended unless the patient's condition is precarious.*

The Use of Blood Transfusions in the Treatment of the Anemia of Chronic Infection.—This type of anemia is exceedingly common and hence should be considered as one of the most important blood disorders which is encountered in clinical medicine. It has two characteristics both of which are constant in occurrence namely (1) it is usually mild in degree is rarely is the hemoglobin less than 7 8 grams per 100 cc (50 per cent) and (2) it is completely refractory to all forms of therapy except the removal of the cause and blood transfusions.

There is no doubt in my mind but what blood transfusions are indicated in this condition more frequently than they have been in the past. This is because although the anemia may be mild it is productive of symptoms such as weakness and dyspnea on exertion. Furthermore by giving blood transfusions it may be possible in some patients to increase the defense mechanisms of the body to a point where the infection is controlled. The effect of such therapy on a patient with rheumatoid arthritis for example may be most beneficial when employed in conjunction with other therapeutic measures. The value of multiple blood transfusions in other types of chronic infections such as those involving the urinary or respiratory tract has been demonstrated. This convinces me that they should be used more frequently in these conditions as well as in other types of chronic infections.

Transfusions are of value in the treatment of infections if for no other reason than the favorable effect they exert on the commonly associated anemia. Clinical experience has shown that they improve the general condition of the patient and with this it is a reasonable assumption to consider that the resistance of the patient is also increased.

determine the blood type of all patients with pernicious anemia in whom the red blood cell *count is 1 0 million per cubic millimeter* or less and make all arrangements for an immediate blood transfusion if the occasion arises

Blood transfusions are undoubtedly a life saving measure in the pre operative and postoperative treatment of patients Certainly they must be considered as one of the most important factors in rendering major operative procedures less hazardous and also less disturbing to the patient In a large hospital it is estimated that approximately one half or even more of the blood transfusions are given immediately before or after major surgical procedures have been carried out It has been clearly established that blood transfusions can convert a poor operative risk into a good one and that postoperative transfusions undoubtedly are life saving in many instances Statistical evidence from all of the more important surgical clinics in this country indicate that blood transfusions are of such value that they are administered in a large percentage of cases either before during or after the operation Their value has been so adequately established that major surgery should not be attempted without having adequate facilities for administering blood transfusions in any number promptly and safely to any patient in whom the indications arise It is my opinion that unless a major operative procedure is urgent it should be deferred if an anemia is present until the hemoglobin is at least 11 0 grams (70 per cent) or higher

Transfusions as a Means of Expediting the Return of the Blood to Normal in a Patient with Anemia —It has been argued in the past by some that blood transfusions should be given to patients who have developed an anemia from any cause which can be controlled as a means of accelerating the return of the hemoglobin and red cell count to normal An example of the situation in which this is advocated would be in a patient with a bleeding peptic ulcer in whom the medical treatment had been instituted and all evidence of bleeding had ceased It is known that under these circumstances with proper iron medication the hemoglobin will regenerate at the rate of about 1 per cent a day until a normal level is reached If for example the hemoglobin was 50 per cent as the result of bleeding which had been controlled then the blood should reach a normal level of 85 per cent in approximately 35 days This same situation would apply to a female who had suffered a large uterine hemorrhage following an abortion after the bleeding had ceased

In recent years I have been inclined to give one or more blood transfusions in order to expedite convalescence It is known for example that a blood transfusion of approximately 500 cc will raise the hemoglobin of the circulating blood about 10 per cent If a patient therefore with a hemoglobin level of 50 per cent as a result of hemorrhage is given three blood transfusions of 500 cc each every other day his hemoglobin

pathological bleeding In general it may be said that they are of value in those conditions in which there is a deficiency of any one of the essential factors in the clotting process Reference to the diagram admittedly incomplete which is based upon the classic theory of blood coagulation is of value in understanding the control of hemorrhagic diseases from a therapeutic point of view

(1) Prothrombin (in plasma)	+	Thromboplastin (in platelets tissues and possibly plasma)	+	Calcium (in plasma)	=	Thrombin
2) Thrombin	+	Fibrinogen (in plasma)			=	Fibrin (Final Clot)

Although theoretically a deficiency of any of the above factors might be of importance in abnormal bleeding from a practical standpoint it is recognized that changes in only two namely prothrombin and thromboplastin or its precursors are encountered frequently enough to be of practical importance A third a deficiency of fibrinogen either acquired or congenital is recognized but it is exceedingly rare The fifth factor of Owren (see page 536) may be encountered occasionally and this may be controlled at least temporarily by blood or plasma transfusions

It is known that abnormal bleeding due to a hypoprothrombinemia may be associated with a severe dietary deficiency in conditions of intestinal disease and malabsorption in the newborn infant as a result of a prothrombinemia except in the varieties associated with hepatic disease and in obstructive jaundice Vitamin K is effective in all types of hypoprothrombinemia except in the varieties associated with hepatic disease and possibly the type due to dietary deficiency It has been shown by Bollman Butt and Snell (55) that vitamin K is not likely to elevate the plasma prothrombin or control the hemorrhagic tendency if liver damage is severe Furthermore it is said that the latent period before the effect of vitamin K therapy decreases the bleeding tendency is occasionally too long even in patients with normal hepatic function (56) In such cases *the transfusion of whole blood or plasma is the only effective means of increasing the plasma prothrombin and controlling the hemorrhagic state* If administered in adequate amounts it is possible by this means o control even the most severe prothrombin deficiency

As pointed out by Ross (56) it should be remembered that prothrombin is a labile substance which is rapidly destroyed in alkaline solutions and in blood and plasma stored at room temperatures Prothrombin activity is more slowly lost in blood or plasma stored at 4 degrees C Plasma separated promptly from drawn blood and frozen immediately retains almost all of its prothrombin activity for several months Although prothrombin is preserved in desiccated plasma it may be de

In addition to the weight of clinical experience which favors the view that blood transfusions are beneficial in the treatment of infections excellent evidence in support of this belief is available in the work of Pastore (*51*) dealing with the relationship of postpartum hemorrhage to puerperal infection His observations show a definite correlation between the amount of blood lost at delivery and the incidence of infection For example he has determined that patients whose blood loss at delivery amounts to approximately 0 3 per cent of the body weight (180 cc in patients weighing 60 kilograms) the incidence of puerperal infection in his series was 6 5 per cent If the loss is greater than 1 5 per cent of the body weight (900 cc in a person weighing 60 kilograms) 32 per cent of the patients developed puerperal infection Hence it appears to be true that the greater the loss of blood the higher the incidence of puerperal infection

It has been shown by Kolmer (52) that certain specific and non specific antibacterial and antitoxic substances may be transferred by transfusions of fresh blood or plasma and according to this investigator may be of considerable value in the treatment of infections and infectious diseases Convalescent serums and immune globulins have proven successful in the treatment of such infections as scarlet fever measles mumps and pneumococcal infections

It has not been established that the transfusion of leukocytes which are present in the blood of the donor is of value in combating infections although the possibility that they may function in this respect cannot be completely dismissed It was at one time thought that blood trans fusions by supplying leukocytes might be of value in the treatment of agranulocytosis and some still hold to this view Most observers believe however that there is no conclusive evidence in support of it at present It is not possible to demonstrate that the white blood cell count of the recipient is elevated by blood transfusions Although it is known that the immune globulin substances are quite stable it is also recognized that complement leukocytes and possibly other important antibacterial substances rapidly degenerate in stored blood (*53 54*)

My own impression is that blood transfusions are certainly of value in combating infection in the presence of an anemia Careful consideration therefore should be given in every case with an anemia to the possi bility of administering a sufficient number of blood transfusions to bring the blood to approximately normal In the presence of a normal hemo globin and red blood cell count however in a patient with an infection I do not believe that the evidence is clear enough at present to cause me to give either blood or plasma transfusions This is particularly true now that such valuable means as the sulfonamides and various anti biotic preparations are available for the treatment of infections

The Use of Blood Transfusions in Hemorrhagic Diseases —Blood trans fusions are a simple and effective method of controlling several types of

milligrams of ACTH subcutaneously every six hours or 75 milligrams of cortisone orally every six hours. Within 36 to 48 hours there is almost always an increase in the number of platelets and a control of the bleeding. Blood transfusions are employed in such patients only when bleeding due to the thrombocytopenia has been severe enough to cause an anemia of importance. Ultimately a high percentage of such patients must undergo a splenectomy which will cure approximately 80 per cent of them.

Patients with *secondary thrombocytopenia*, however, in association with a primary disease such as leukemia or aplastic anemia, are not benefited by the use of ACTH or cortisone. In fact, the purpuric manifestations in such patients present a difficult therapeutic problem. The therapeutic aims are to control the underlying disease, if possible, and to give blood transfusions to control the anemia. *In my experience, however, it has not been possible to transfuse blood platelets successfully.* The life of the platelet is short, approximately four to six days according to Hirsch and Gardner (60) and in idiopathic thrombocytopenic purpura it is probably 24 hours or less. Furthermore, it has been shown by Lawrence, Valentine and Adams (61) that the platelet level of the peripheral blood cannot be elevated significantly for any length of time by means of direct massive transfusions of blood. It is possible that by using a platelet rich blood which may be obtained from an untreated polycythemic donor that the circulating platelets may be increased in the recipient but this is not a very practical means of coping with the situation (see section on treatment of purpura, page 642).

Treatment of Shock Associated with Hemorrhage.—The fundamental difficulty which must be met immediately if a patient has advanced far enough in the state of shock, either with or without hemorrhage, is the reduction in blood volume. In this respect the treatment of shock is the same, regardless of the cause. The acute loss of an extremely large amount of blood, such as 30 per cent of the total blood volume, usually results in death unless immediate steps are taken to restore the blood volume to a more nearly normal level. If, for example, a male weighing 70 kilograms who would have a calculated normal blood volume of 90 cc. per kilo or 6300 cc. lost one third of his blood or 2100 cc. from acute bleeding, death would be imminent. On the other hand, it is estimated that some patients in shock may have a reduction in blood volume of 50 per cent due to surgical shock either with or without hemorrhage. Such patients, however, are gravely ill and the condition usually terminates fatally. It is not infrequent, however, for patients in shock with a 25 per cent reduction in blood volume to make a complete recovery.

When shock is due to hemorrhage, the treatment is immediate transfusion with a sufficient quantity of blood to restore the blood volume to such a level that the ominous symptoms are controlled. It should be pointed out that in a person with a blood volume of 6000 cc. there must be

stroyed during reconstitution if the reaction is not maintained near neutrality (57) Reconstitution of desiccated blood plasma with a 0 1 per cent solution of citric acid, instead of with distilled water is said to maintain the reaction of the plasma near neutrality and preserve a satisfactory prothrombin content (56)

The Control of Bleeding in Patients with Hemophilia —The clotting defect in patients with hemophilia is due to a deficiency of thromboplastin which has been attributed either to an abnormal resistance of the blood platelets or to a defect in the plasma itself The control of bleeding in patients with this disease is accomplished by the injection of whole blood freshly drawn citrated blood or plasma

It has been shown that the plasma of normal blood contains a substance effective in reducing the coagulation time of hemophilic blood to normal and that this substance is associated with the globulin fraction (58) Evidence has been presented by Johnson (59) to indicate that plasma desiccated in a partial vacuum at a low temperature maintains its ability to reduce the coagulation time in hemophilia similar to that of fresh citrated blood It is also said by Johnson (59) that storage of the processed plasma does not destroy its thromboplastic activity The material which is effective in accelerating the clotting process in hemophilia is apparently quite stable and is well preserved in blood or plasma kept at 4 degrees C and in frozen and desiccated plasma (56)

In the management of patients with hemophilia the method of choice however based upon the longest experience is to give citrated blood in amounts of 250 to 500 cc until the coagulation time approaches normal It will usually remain in such a condition for a period of four days during which time even a major operation may be accomplished It is true that smaller blood transfusions (50 to 100 cc) may be of some benefit but it may be advisable to administer larger amounts on account of an associated anemia due to hemorrhage Furthermore the advantages of this is that the results are usually more decisive and persistent

Johnson concludes (59) that lyophile plasma which has been frozen and dried within a few hours after removal from the donor decreases the coagulation time in hemophilia and that the thromboplastic activity is preserved for at least three months when the plasma is kept at 5 degrees C (For further details on the treatment of hemophilia see page 595)

The Control of Thrombocytopenic Purpura —One of the most difficult therapeutic problems encountered in hematology is the control of bleeding when it is associated with thrombocytopenia In recent years however this has been simplified somewhat by the introduction of ACTH and cortisone which almost always favorably influences the number of platelets and the bleeding in the *idiopathic* type Hence any patient with bleeding due to this condition should be treated promptly with 25

years this belief caused me to proceed cautiously with blood transfusions in patients with bleeding which was not accessible to surgical control. Such a condition would be, for example, a bleeding peptic ulcer. Some years ago I abandoned this belief when I was able to demonstrate to my satisfaction that the blood pressure was not increased importantly following the injection of blood even when it was given at a fairly rapid rate.

If whole blood is not available for administration, it is advisable to give serum or a blood substitute in acute hemorrhage although in my opinion, as previously stated, these forms of therapy are inferior to whole blood. The use of blood from the blood bank has the advantage of placing large amounts of tested and typed blood at the physician's disposal at a moment's notice which may save a patient's life.

Treatment of Traumatic or Secondary Shock without Associated Hemorrhage.—Whatever may be the primary cause of secondary or traumatic shock, it seems to be generally agreed that (1) the essential and fundamental feature of this condition in some patients at least is the escape of an excessive amount of plasma from the vascular system as the result of an abnormal permeability of the capillary walls with concentration of the blood and a reduction in the total blood volume, and (2) furthermore, it is the general belief that the restoration of blood and plasma volumes in order to maintain an adequate circulation is the therapeutic indication of first importance.

In World War I, studies by Cannon, Fraser and Hooper (62) showed that two thirds of the soldiers in shock had a red blood cell count in the capillaries of six millions per cubic millimeter or higher, in one third seven millions per cubic millimeter or higher, and in one sixth, eight millions per cubic millimeter or higher. The difference between the capillary and the venous red blood cell count was conspicuous, as in the more severe cases it amounted to as much as two millions per cubic millimeter, and in those with moderate shock it was a million per cubic millimeter. Since the venous count in these patients was normal, it is obvious that there was striking concentration or stasis in the capillaries.

In the treatment of surgical shock without associated hemorrhage, it appears that plasma or serum is the ideal form of fluid for intravenous injection. It certainly would be harmless as far as causing additional *concentration of the red blood cells is concerned*; it can, moreover, be administered more rapidly, as typing is not necessary, and it is more convenient to give under conditions of warfare and in many instances in civil life. On the other hand, if plasma is not available, it is probably advisable to administer whole blood despite the fact that hemoconcentration is present in the patient. This is because the injected blood from the donor is of normal concentration with a red blood cell count of 5.0 millions per cubic millimeter or less and a hematocrit reading which

a reduction in blood volume varying between 1500 and 2100 cc (from 65 to 75 per cent of normal) in cases in which the condition of shock is well advanced This requires the administration of 1250 to 2500 cc of blood and in some instances even more This is emphasized because in the past it has been considered erroneously that if one transfusion of 500 cc is given then the therapeutic indications have been met adequately While this amount of blood is helpful it is apparent from the figures just given that a larger quantity is indicated if the maximum therapeutic effect is to be attained

It is my opinion that the best results in shock due to acute hemorrhage are to be expected if whole blood is given instead of plasma or some blood substitute This is for two reasons as follows (1) In the first place *in such patients there has been a severe loss of hemoglobin* and red corpuscles Their immediate replacement will be of assistance in restoring the hemoglobin and the red blood cell count to normal at the earliest possible moment (2) If plasma or some blood substitute were injected it would cause further dilution of an already strikingly reduced hemoglobin content and hence increase the anoxemia

While I do not regard the reduction of hemoglobin as the main cause of death in these patients as this is usually attributable to the reduction in the blood volume nevertheless, the rapid development of a pronounced anoxemia which must be associated with low hemoglobin levels is a hazard which should be constantly kept in mind Although all clinicians have had the opportunity to observe patients who seem to carry on remarkably well even with hemoglobin levels below 20 per cent in these patients the reduction in hemoglobin has usually resulted from various factors which have been acting for a long time and this prolonged interval has permitted the body to adjust itself to this change In acute hemorrhage the situation is quite different as only a short interval exists between the reduction in the hemoglobin and red blood cells from a normal level to one which is strikingly low

When shock due to hemorrhage is present at least 1000 cc of blood should be given at the rate of 250 cc to 500 cc per hour or much faster if the patient s condition is precarious In an emergency 500 cc may be given within five to 10 minutes and a second equal amount in the next 25 to 30 minutes When substantial evidence of improvement appears an additional 500 cc to 1500 cc should be administered at the rate of approximately 250 cc per hour or more depending upon the level of the blood pressure on the patient s condition and the general response to therapy

In acute hemorrhage it has been said that transfusions should be withheld on the grounds that they may raise the blood pressure and hence might dislodge a clot and cause the hemorrhage to be resumed or to augment the loss of blood which has lessened For a number of

of the lost fluid should be based primarily upon this factor They believe that the formula based on the hematocrit reading as devised by Harkins (64) is simple and the least conducive to error in rapid calculations during emergencies It was his suggestion that 100 cc of plasma be given for every point that the hematocrit is above normal

It is suggested by Presman (63) that following severe burns in adults for every per cent of the body surface which is burned 50 cc of serum be given immediately and in addition 20 to 30 cc during the first 24 hours and another 20 to 30 cc during the next 48 hours They do not advise the administration of crystalloid fluids during the first 24 hours after the burn but do make the logical recommendation that fluids and a high protein diet be given as soon as the patient is able to take food by mouth According to their recommendations therefore the total administration should be at least 100 to 110 cc of plasma for each per cent of the burned area of the body

It is of interest to note that these investigators found that blister fluid contains a concentration of proteins equivalent to 70 to 80 per cent of the plasma proteins They noted that the albumin content of blister fluid is fairly constant but the globulin content showed pronounced variations independent of the albumin or globulin values of the blood and of the albumin content of the blister fluid

An additional point of interest from a therapeutic standpoint in patients with extensive burns is the observation of Shen and Ham (65) that hemoglobinuria either gross or minimal may occur in persons receiving combined second and third degree burns involving 15 to 65 per cent of the body The patient s plasma in such cases usually shows hemoglobinemia and spectroscopically it is often possible to demonstrate the presence of oxyhemoglobin mixed with traces of methemoglobin

The observation was made by these investigators that if blood is rapidly heated to a temperature of 51 to 65 degrees C striking changes occur in the red blood cells These consist of fragmentation and the formation of spherocytes and microspherocytes It is their belief that the increased osmotic fragility of heated red blood cells apparently results from conversion of the normal biconcave erythrocytes to the more nearly spherical forms by a process of progressive fragmentation They suggest the possibility that the destruction of the red blood cells is a result of the increased fragility in vivo This occurs through a mechanism of swelling and is followed by osmotic hemolysis in the plasma of the animal It is significant to note that although a certain number of red blood cells are destroyed in patients with extensive burns anemia is not common at least as an early development The indication in the treatment of such conditions is not therefore to transfuse whole blood On the other hand if plasma is not available it is permissible to give whole blood even though the recipient s hematocrit is elevated As

averages about 45 per cent. This fluid when injected into the veins of a patient in shock who has concentrated blood will cause some dilution.

In summary, therefore, it should be said that the proper treatment of traumatic shock without hemorrhage is the injection of 1250 to 2500 cc of citrated plasma or reconstituted desiccated plasma in equivalent amounts. The use of desiccated human or animal albumin and certain blood substitutes will be considered under the heading of the value of blood substitutes. If it is not possible to obtain plasma, then it is advisable to inject whole blood, although it has the disadvantage of adding red blood cells to the recipient's blood in which the red blood cell count is already above normal. As the injected blood is more dilute than the blood of the recipient, it will, of course, reduce the concentration of the blood of the latter to some extent.

The Use of Whole Blood and Plasma Transfusions in the Treatment of Shock Associated with Burns.—It has been demonstrated that the chief cause of death in extensive burns is shock which arises as a result of the loss of fluid from the vascular system with a resultant diminution in the blood volume. It is considered by some that the fluid loss is not entirely due to the leakage from the capillaries in the burned areas and the tissues immediately surrounding it. Among those who contend that it is lost from the circulation elsewhere in the body are Presman and his associates (63). It is their belief that there is a considerable loss of fluid and of protein from the blood due to secondary changes in capillary permeability in other areas of the body. They state that in animal experiments the scalding of even a very small part of the body is usually followed by degrees of hemoconcentration which cannot be explained by local loss of fluid in the injured area.

All are in agreement that following extensive burns, the body is severely depleted of fluids and protein, and that a fatal issue is averted and recovery expedited by the immediate injection of large amounts of fluids intravenously. As it is the loss of fluid and protein which is responsible for the condition of shock in patients with burns, it appears logical to replace the material which is lost from the circulation with plasma. In such patients, therefore, the immediate therapeutic indication is the injection of a suitable amount of blood plasma in order to restore the blood volume to approximately normal.

The amount of plasma to inject is a question about which there is some disagreement. It has usually appeared to me, as previously stated, that in shock due to any cause the tendency has been to give too little, especially in the early days of the use of intravenous fluids to combat shock. Recently Presman and his associates (63) have advocated, along with others, that as in man the amount of fluid lost is proportional to the extent of the body surface burned, then the formula for the replacement

prehensive review dealing with this subject by Edwin J Cohn appeared in the *American Scientist* of April 1945 (38) and is complete to that date

For the present only a brief resume of our present knowledge concerning this subject will be given by the tabulation of the more important substances which have been used as intravenous injections including citrated blood blood derivatives and blood substitutes Brief comments only will be made concerning the more important points in favor or against the use of the various materials listed

BLOOD, BLOOD DERIVATIVES AND BLOOD SUBSTITUTES WHICH ARE USED FOR INTRAVENOUS INJECTION

I Blood

1 Unmodified is used for direct transfusion or by the syringe method

2 Citrated

a Fresh administered at once or only after a few hours of refrigeration at 5–10 degrees C

b Stored after collection in sodium citrate and injected after more than several hours of storage should not be used after the fifth day on account of the changes which occur

c Preserved blood which is collected in an A C D (acid citrate dextrose) mixture and stored for a period of 21 to 28 days at a temperature of 5–10 degrees C

3 Red blood cell transfusion consists of the injection of red blood cells separated from 60 to 80 per cent of the plasma and resuspended in chilled saline solution (0 85 gram to 100 cc)

II Plasma

1 Plasma transfusion administration of the cell free supernatant portion of whole blood collected in A C D diluent or sodium citrate solution

2 Dried plasma to be reconditioned by sterile distilled water so that its constitution is approximately the same as fresh plasma

3 Frozen plasma separated from cells and frozen within 72 hours may be stored almost indefinitely but should be injected *promptly after thawing*

4 Fractions I and V of Cohn prepared according to the methods developed by E J Cohn and his associates (67) and Mulford (68) Fraction I contains fibrinogen and the antihemophilic globulin Fraction V the albumins of plasma which are chiefly responsible for its osmotic activity

previously stated the concentration of the donor's blood will be less than that of the patient's

The Use of Blood Transfusions and Plasma as a Means of Providing a Form of Protein for the Blood Stream—*In recent years the possibility that the blood proteins could be increased by the* administration of blood intravenously in patients with hypoproteinemia has been emphasized Undoubtedly the intravenous injection of various substances in the treatment of hypoproteinemia is of great importance and many studies bearing on this in the near future will most certainly be productive of advances in this field When intravenous injections are given for this purpose, however the essential part of the blood is the plasma The red blood cells are not only valueless for this purpose but often they are even objectionable The treatment of hypoproteinemia by means of the blood substitutes will be discussed under these headings which follow

The Blood Bank and a Consideration of the Derivatives and Substitutes for Blood Which Are Administered Intravenously—The stimulus of the recent wars has resulted in rapid advances in the field of transfusions, largely on account of the realization that they are the most effective means of treating one of the chief causes of death in warfare namely shock *In the first World War there were three major additions* to our knowledge concerning the state of shock which served as a starting place for the present advances in this conflict They were (1) the recognition that the chief basis for the condition is a pronounced decrease in the volume of blood in the body (2) the demonstration that certain substances such as blood transfusions and intravenous injections of acacia solutions could produce changes in the intravascular osmotic pressure relations and thereby augment the blood volume and (3) the realization that citrated blood could be preserved at least for several days and administered apparently with advantageous effects This marks the beginning of the modern blood bank to which full credit should be accorded to Dr Oswald Robertson Professor of Medicine at the University of Chicago His experiences are recorded in a brief article published in the *British Medical Journal* for June 22 1918 (66)

The remarkable feat performed by the American Red Cross of collecting large amounts of blood throughout the United States the preparation of huge quantities of dried plasma which has been shipped all over the world for use by our armed forces the study of the effects of various blood substitutes and the large scale attempts to fractionate human plasma have all served to direct attention of the public and the medical profession to this field Consequently many advances have been made and many others still await study Hence new and important further advances are likely to be made A most comprehensive group of articles dealing with the early studies of protein fractions of human plasma appeared in the *Journal of Clinical Investigation* for July 1944 A com

prehensive review dealing with this subject by Edwin J Cohn appeared in the *American Scientist* of April 1945 (35) and is complete to that date

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II PLASMA

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III SERUM
1 Liquid
2 Frozen
3 Desiccated (Serum differs from plasma as it does not contain fibrinogen, for technical reasons plasma is easier to process and is equal or superior to serum in all other aspects)

IV GELATINE SOLUTIONS (69, 70 71) animal gelatine may be given intravenously when properly prepared, *it is the best of the plasma substitutes* but inferior to blood and its substitutes Fish gelatine (isinglass) is equivalent in its effects to animal gelatine

V OTHER PLASMA SUBSTITUTES
1 Acacia (72) has the same disadvantages as gelatine as it is *deposited in the body tissues and hence it is potentially harmful*
2 Solutions of human hemoglobin (73 74) have been used in the treatment of shock but their toxic effects are contraindications to their use
3 Globin (75) prepared from human hemoglobin has been shown to be valuable in experimental animals but is not established as a form of successful treatment in humans
4 Pectin (76) has similar effects in shock and on the red blood cells as gelatin as it is in part, at least deposited in the tissues of the body it must be regarded as potentially dangerous
5 Methylcellulose (77) is of value experimentally in the treatment of shock *in animals but its use in humans* is limited because it causes renal damage
6 A miscellaneous group of substances including bovine albumin and beef blood plasma (78 79) have been employed as blood substitutes but their use is not recommended Amino acid mixtures likewise have been employed in shock in experimental animals and in humans (80) but their value has not been demonstrated at present Ascitic fluid has been used (81) and it is possible to administer it intravenously without untoward effects after it has been stored in the ice box for 24 hours or more As its protein content is about one half or less that of plasma it is not especially valuable in treating patients with shock or hypoproteinemia

Summary of Indications for Use of Blood and Blood Substitutes, and the Preparations of Choice —The following paragraphs are based in part on the table dealing with this subject prepared by DeGowin and his associates (82)

The preference for first choice in the treatment of *hemorrhagic shock* is first, fresh and preserved whole blood second liquid frozen or dried plasma For the treatment of *shock in association with burns or due*

to the crush syndrome it is first liquid frozen or dried plasma second fresh or preserved whole blood In patients with *medical shock* in such conditions as Addison's disease diabetic coma and diarrhea in infants it is recommended that plasma in the liquid frozen or dried forms be given preference second fresh or preserved whole blood In *hypoprothrombinemia* the most satisfactory treatment is with fresh liquid plasma or fresh whole blood In *hemophilia* the most effective therapy is fresh whole blood and second antihemophilic globulin and third

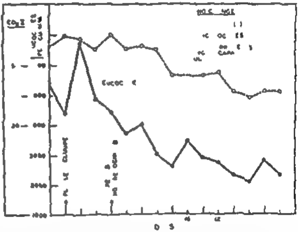

Fig 77 —Changes in "stored citrated blood which was maintained at a temperature of 4 to 8 degrees (C) for 17 days to which glucose had not been added With minor fluctuations the red blood cell counts and hemoglobin content remained remarkably constant When sodium citrate was used alone hemolysis was noted after 48 hours and after 96 hours the fragility test was of no value in determining the onset of hemolysis In blood stored under similar circumstances except that glucose to the extent of 10 cc of a 5 4 per cent solution per each 100 cc of blood was added the degree of hemolysis was slight and the fragility test could be used satisfactorily as an indication of the tendency of the erythrocytes of hemolyze Regardless of the type of preservative used the white blood cells deteriorated within 48 to 96 hours The lymphocytes and monocytes appeared to be the most stable After 72 hours a leukopenia was noted and the white blood cell count decreased progressively There was clumping of the platelets within 24 hours after the blood was drawn which soon became more pronounced The reticulocytes remained constant There was no change in the blood type or titer The plasma proteins oxygen capacity and non protein nitrogen were unchanged The carbon dioxide combining power maintained a constant level for eight days and thereafter gradually decreased In the samples without added glucose it was found that the blood sugar remained constant for about 24 hours and then decreased rapidly reaching its lowest value on the sixth day (Goldhamer Fritzell and Findley courtesy *University Hospital Bulletin* University of Michigan)

liquid frozen or dried plasma In the treatment of *infection by immunotherapy* it is recommended first that liquid plasma stored less than three months be used or frozen or dried plasma may be given second choice is fresh or preserved whole blood In *acute hypoproteinemia* concentrated human serum albumin or dried plasma are the preparations recommended I am in accord with the conclusion that no therapy with blood or blood derivatives or substitutes is worth while in patients with chronic hypoproteinemia or with leukopenia or thrombocytopenia

THE BLOOD BANK

Changes Which Occur in Preserved Blood.—The Red Blood Cells.— It is of great importance to determine the length of survival of the erythrocytes after they have been injected into the veins of the recipient following various intervals of storage at 5 to 10 degrees C. when a *purely anticoagulant preparation or an A.C.D. (acid citrate dextrose)* mixture has been used for preservation. The information available concerning this has been recapitulated by Mollison (*83*). He states that with trisodium citrate alone, the red blood cell survival in the recipient is almost (90 per cent) as good as fresh blood provided the blood injected has not been stored for more than three days; the red blood cell survival is only about 70 per cent as good as fresh blood if the storage period has been six days. From these figures, therefore, if citrate only is employed, it is advisable to use the blood immediately or not to store it for longer than *three days*, or *six days* at the most.

The introduction of A.C.D. mixtures as a means of preserving blood was of great assistance in improving the efficiency of blood banks. For example, quoting the results cited by Mollison (83), red blood cell survival in the recipient is at least 90 per cent as good as fresh blood when an A.C.D. mixture is used as a preservative, provided the blood has not been stored for longer than *14 days*, and is 70 per cent as good as fresh blood if it has not been stored for more than *24 days*. From *these figures it may be concluded that* blood preserved by this method and stored at an optimum temperature range between 4 and *10 degrees* C. in an A.C.D. mixture should be used before a 14-day period of storage, when the red blood cell survival period in the recipient would be 90 per cent as good as fresh blood, or at least before a 24-day period, at the end of which time the red blood cells survival would be only 70 per cent as good as fresh blood.

Effect of Storage of Blood on the Leukocytes.—All investigators are in accord with the statement that the white blood cells begin to show the early changes of disintegration within 24 to 36 hours after the *blood has been drawn into dextrose citrate solution* and *preserved* under proper conditions of refrigeration. Within four to five days these changes usually progress to such a degree that a correct differential count is impossible. It has been concluded by Crosbie and Scarborough (*84*) that there is a loss of 11 per cent in the leukocytes on the first day, 17 per cent on the second day, 22 per cent on the fourth to fifth day and 24 per cent on the sixth to the tenth day.

It has been shown by Shamov (*85*) that phagocytosis is preserved to some extent in cadaver blood for as long as 11 hours. Additional information in regard to the activity of the leukocytes is found in the studies of Karavanov (*86*) who observed that the polymorphonuclear leukocytes retained some of their phagocytic activity after five or six

days of storage but that it declines sharply after the second day It appears certain therefore that the time of survival of the leukocytes with the preservation of their physiologic function in stored blood is very short

The importance of the role of transfused leukocytes in combating infection is not yet known According to Kolmer (52) donor leukocytes may be of assistance in overcoming some types of infection although it is not possible to demonstrate that the recipient's white blood cell count can be elevated by blood transfusions As the degenerative changes in the leukocytes occur so early when blood is stored even under the most ideal conditions which are known at present it is not likely that the leukocytes of bank blood provide additional assistance to the body in overcoming any infection which may be present It is the opinion of Jackson and Parker (87) that blood transfusions even of fresh blood are of little value in the treatment of agranulocytic angina From the standpoint of supplying white blood cells to a patient with this condition bank blood would be even of less value

It is known that the immune globulin substances are quite stable and hence are preserved in bank blood but that complement and certain antibacterial substances rapidly degenerate under these conditions

The Blood Platelets in Bank Blood—The platelets are the earliest morphological components of bank blood to degenerate and hence at the same time probably become functionally inefficient It has been found by Drew and Scudder (68) that the platelet count falls to less than 100 000 per cubic millimeter in 24 hours in stored blood and to about 40 000 per cubic millimeter in three days Kolmer (69) and Belk and his associates (90) are in accord with this statement It has been reported by Dubash Clegg and Vaughan (91) however that the platelets are maintained at a fairly constant level of 40 000 per cubic millimeter even after 14 days of storage in a citrate dextrose mixture

In general it may be said that the evidence available indicates rapid degeneration of the blood platelets which probably make them ineffective in the treatment of thrombocytopenic purpura either of the primary or secondary types Hence only fresh citrated blood should be employed as a therapeutic agent in this condition

The Effect of Storage on the Prothrombin Time—It should be emphasized that prothrombin is a labile substance which is rapidly destroyed in alkaline solutions and in blood and plasma when kept at room temperatures The activity of prothrombin is lost less rapidly when maintained at a temperature of 4 degrees C. When plasma is separated promptly from freshly drawn blood and is frozen at once the prothrombin activity is preserved for at least several months It is known that prothrombin activity remains in desiccated plasma but that it may be destroyed when the material is reconstituted unless the fluid used for

this purpose is kept near neutrality It is now the practice to reconstitute the dried plasma with a 0.1 per cent solution of citric acid instead of distilled water as such a mildly acid solution is effective in retaining a satisfactory prothrombin content

The findings of Ziegler Osterberg and Hoaig (92) and those of Warner, DeGowin, and Seegers (93) using the prothrombin method of Warner, Brinkhous and Smith are in accord They indicate that the prothrombin content of stored blood diminishes slowly until it reaches a level of about 50 per cent in 21 days After that time the rate of disintegration is somewhat accelerated In general it may be said that stored blood may be used in the treatment of a prothrombin deficiency almost as effectively as fresh blood

Thromboplastin in Bank Blood—It is important to know if thromboplastin is preserved in bank blood for it is a deficiency of this substance which prevents normal clotting in patients with hemophilia The treatment of the abnormal bleeding in patients with hemophilia is the injection of blood intravenously in order that this missing substance may be supplied It is known that the thromboplastin content of the plasma or at least the globulin substance in the plasma of normal persons which controls the bleeding in patients with hemophilia is stable It is well preserved in blood or plasma kept at a temperature of 4 degrees C and also in frozen and desiccated plasma (56)

The Use of Red Blood Cells from the Blood Bank—In obtaining such a large amount of plasma from the blood collected by the American Red Cross through the country in the initial phases of the project, the red blood cells were discarded and only the plasma was used As a result there was a great waste of human material In an attempt to solve this problem, red blood cells thus obtained have been suspended in various solutions and used as blood transfusions in the treatment of anemia by the British workers MacQuaide and Mollison (94) and by Williams and Davie (95) According to Mollison (96) Castellenos (97) was the first to use concentrated suspensions of red blood cells for transfusion purposes It was reported in 1942 by Bagdasarov the Director of the Russian Central Institute for Blood Transfusion (98) that the use of the red blood cell mass was of benefit in the treatment of anemia due to blood loss Alt (99) concluded that the red blood cell transfusions were a satisfactory substitute for whole blood transfusions in the treatment of anemia It was possible for him to maintain a patient with a refractory anemia for a period of one year with repeated transfusions of red blood cell suspensions obtained from a total of 25.5 liters of blood He advanced the argument that because the red blood cells are a by product, resulting from the collection of plasma it is practical to give them more frequently than heretofore has been the practice with whole blood

After studying the use of suspended red blood cells it is stated by Evans (100) that 5 per cent plasma with the cellular portion of the

blood for transfusion is sufficient to allow an even uninterrupted flow with the ordinary recipient set and requires only a somewhat greater force of gravity He reports that single and multiple transfusions with O type of cells have been given with good therapeutic results In his opinion the incidence of reactions does not appear to constitute a greater problem in the use of this type of blood His results indicate that transfusions of concentrated red cells are as efficacious as whole blood in controlling the bleeding tendencies of thrombocytopenia secondary to leukemia This statement is somewhat surprising and requires confirmation

A study of 116 infusions of red blood cell suspensions administered to patients with anemia at the Naval Hospital in Philadelphia has been made by Murray Hale and Shaar (*101*) They describe the technic of preparing the red blood cell suspension in detail as follows the red blood cells which remain after the plasma has been aspirated by means of a closed aseptic technic are used for the preparation of the red blood cell suspension After the plasma is removed the aspirating needle is plunged to the bottom of the red blood cell layer and 200 cc of cells drawn over by means of a vacuum into a sterile 300 cc dispensing bottle which contains 100 cc of 5 per cent dextrose in isotonic solution of sodium chloride The buffy coat which lies between the packed red blood cells and the supernatant plasma is not utilized This contains white blood cells platelets and fibrin The final suspension contains approximately 88 per cent of the red blood cells so obtained from one donation of 500 cc of whole blood These observers employed cells which were from 24 to 48 hours old when they were aspirated into the dispensing bottles They were then stored in a refrigerator at 2 to 5 degrees C for a maximum period of 72 hours after which time those not used were discarded An analysis of the suspension revealed the following average values a hemoglobin of 17 grams per 100 cc a red blood cell count of 6 160 000 and a white blood cell count of 2000 per cubic millimeter

The above authors report that there were only two reactions in 72 infusions given to 42 patients These were pyrogenic in nature one being slight and the other severe There were no hemolytic reactions It is concluded by them that of all the patients requiring blood transfusions in a large hospital probably 50 per cent of them need only red blood cells and hence suspension of red blood cells in the treatment of such patients is of great therapeutic value It was estimated by these observers that the average rise in hemoglobin from each 300 cc suspension was approximately 1 gram and in all but four of the 72 cases studied there was clinical improvement

It has been recommended by Thalhimer and Taylor (*102*) that human type O cells be suspended in a 10 per cent solution of corn syrup and used for transfusion of selected patients According to these authors

it is now recognized that a transfusion of red blood cells can serve as well as whole blood for many patients. The main problem has been to find a solution for resuspension which will preserve the cells for long enough time to make their use practical. These observers have found a 10 per cent solution of corn syrup to be an excellent medium for the resuspension of centrifuged red blood cells. Cells stored in it remain in good physical condition longer than in isotonic solution of sodium chloride and other solutions which were tried. They remain less fragile to hypotonic saline solution and much less hemoglobin is found in the supernatant fluid. Red blood cells resuspended in this medium have been used for transfusion after storage at 5 degrees C for as long as 21 days but for routine use an expiration interval of 14 days is recommended. Seven hundred and sixty one transfusions of centrifuged cells resuspended in corn syrup have been administered by Thalhimer and Taylor with satisfactory results to 437 patients. The transfusions have not been followed by jaundice or other untoward effects. The non specific fever chill rate has corresponded in the different hospitals to that from their own blood bank. Evidence has been produced to indicate that the cells suspended in the corn syrup mixture have survived as long as those in a dextrose citrate mixture stored for the same length of time and longer than cells in isotonic solution of sodium chloride.

There are three conditions according to Mollison (96) in which it may be desirable to use red blood cells suspended in saline rather than plasma. First in patients with an increased venous pressure suspensions are less likely to cause overloading as the saline solution will leave the patient's blood stream more rapidly than plasma. Second in patients who have previously had severe febrile reactions from blood transfusions. It is known as shown by Dameshek and Neber (103) that severe febrile reactions may follow the transfusions of whole blood but these may be averted by the use of washed red blood cells. And third it is desirable to use washed red blood cells in patients with the rare condition of nocturnal hemoglobinuria who are given group O blood if the recipient is of group A or B.

It appears to be demonstrated conclusively therefore that suspensions of red blood cells can be administered without untoward reactions and that when the cells are preserved under the proper conditions they are effective in the treatment of anemia. It is unlikely that this practice will be used to any great extent for aside from salvaging the waste of red blood cells when obtaining plasma which at present must be huge it offers little advantage over the ordinary citrated blood transfusion.

There is risk of infecting the red blood cell suspension but this can be reduced by using a closed system of withdrawal and separating the plasma a few hours after collecting the blood.

The Selection and Protection of the Blood Donor.—Never before in the history of the world has the donation of blood for transfusion purposes

been carried out on such a wholesale basis as during and following World War II This is due to projects of two different types namely the institution and continuation of the blood donor service of the American Red Cross beginning February 3 1941 and the organization of a large number of blood banks in many hundreds of hospitals throughout the country which began in 1937 With this unprecedented donation of blood an excellent opportunity has been afforded to accumulate data on the effect of the removal of blood in amounts of 500 cc at one or more intervals on the health of the donors and to formulate rules and regulations for blood donors which are based on this wide experience

This information was summarized in 1943 by Heiss and Taylor (*104*) based on an extensive experience with donors for the American Red Cross These observers stated that in selecting a donor the matter of eligibility is determined on the basis of a few simple tests and series of questions rather than complete physical examination which is usually not feasible either in selecting donors for the blood bank of a hospital or the Red Cross project The following regulations were in force by the American Red Cross at the time of the report by Heiss and Taylor (1) Donors outside the limits of 21 to 60 were not ordinarily accepted those under 21 years of age were not utilized without the written consent of the parents or guardian (2) Donations might be given by individuals every eight weeks but not more than five donations were permissible in any twelve month interval (3) No donor was acceptable if the body temperature orally exceeded 99 5 degrees In my opinion a body temperature reaching this height is indicative of either some pathological condition or an exceedingly high strung nervous person, neither of whom are qualified to act as donors at the time hence their use should be deferred The upper limit of body temperature indicating a state of health is 99 degrees F (4) A donor was not accepted unless the hemoglobin level was 80 per cent or above by the Tallquist method More recently however the copper sulfate method of estimating hemoglobin has been used all donors are required to have a hemoglobin of 12 3 grams per 100 cc or higher (5) A donor was not accepted unless the systolic pressure was between 100 and 200 millimeters of mercury The Red Cross quite correctly refuses to accept the responsibility of accepting donors with hypertension on the basis that venesection might be a useful therapeutic measure Any cardiovascular complication which might arise soon thereafter might be interpreted as a harmful effect due to the removal of blood (6) The pulse was recorded and a note made of irregularities as well as of bradycardia and tachycardia I do not know just what bearing this might have on the desirability of any person acting as a blood donor except that a rapid heart rate might give some indication of the state of the nervous or circulatory system, or in some instances suggest that a patient had an elevated basal metabolic rate

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The Selection and Protection of the Blood Donor.—Never before in the history of the world has the donation of blood for transfusion purposes

carbon dioxide through the lungs and the production of tetany (It is worthy of note that in the experience of the Red Cross that an appreciable number of cases of coronary thrombosis have been observed with the acute symptoms occurring within five to 48 hours following a blood donation.) A few cases of mild congestive heart failure, and cerebral embolism have also been encountered It must be remembered, when discussing such accidents that they have been relatively few considering the very large number of donors who have served the Red Cross since 1941 In my opinion it is not possible to say that the association of these conditions with the removal of 500 cc of blood from the body is anything more than a coincidence) It is to be expected that syncope usually attributable to nervous tension will always be present in a certain number of patients This in itself is of little importance provided the proper precautions are taken to protect the patient from trauma due to sudden collapse

In a more recent paper Boynton and Taylor (*105*) make the statement that with a controlled basis of operations for all procedures and a rigid eligibility standard for all donors the withdrawal of 500 cc of blood from normally healthy individuals should offer no serious potential hazard to the donors The experience of the American Red Cross Blood Donor service to date has confirmed this assumption Approximately 9 per cent of the donors experienced some form of transient reaction during or immediately following the donation The symptoms encountered in order of frequency were as follows pallor 93 per cent perspiration 69 per cent nausea 28 per cent loss of consciousness 11 per cent *vomiting 4 6 per cent convulsions 3 4 per cent twitching 2 1 per cent* cramps 1 9 per cent tetany 1 0 per cent incontinence 0 5 per cent There were 34 donors of 2294 with reactions who developed the symptoms and signs of shock sufficiently severe to require hospitalization for observation and on a number of occasions it was thought wise to autotransfuse donors who had a severe reaction It is of interest to note that 4 per cent of all individuals who donate blood experience some limitation of their activities during the week following the donation It is thought that these persons consisted largely of women who may not have regenerated their hemoglobin with normal rapidity The possibility arises that previously these patients had a hemoglobin in the circulating blood which was too low but this was not detected by an inaccurate method which has now been corrected

A statistical study of the causes for rejection of blood donors covering a period of seventeen months at the Chicago Blood Donor Center which is concerned with 375 768 donors (42 27 per cent males and 57 73 per cent females) has been made by Zukerman (*106*) During this time repeat donors averaged between 48 and 62 per cent Of the total number who offered themselves for donation of blood there was a rejection rate

In addition to these logical regulations the following brief history (*104*) is elicited from all prospective donors

1. Have you had any illness in the last month?
2. Have you any chronic illness?
3. Have you had malaria within the past 15 years?
4. Have you ever had clinical pulmonary tuberculosis?
5. Do you have diabetes?
6. Did you ever have shortness of breath?
7. Do you ever have swelling of the feet?
8. Do you have a persistent cough?
9. Do you ever have pain in the chest?
10. Have you coughed up blood recently?
11. Do you have fainting spells?
12. Did you ever have convulsions?

No donor is accepted by the Red Cross who has recently had a sore throat or recovered from any infection The advisability of utilizing persons with chronic infections is left to the discretion of the physician present It is the policy of the Red Cross to accept persons with hay fever and the common allergies since the processing of blood into plasma is accomplished by the pooling of 25 to 50 donations of blood In my opinion in collecting blood for a blood bank persons with definite allergic manifestations of any type should be rejected as donors on the grounds that the recipients might experience allergic reactions

It is the policy of the Red Cross to reject all prospective donors who have ever had malaria within the past 15 years those who have ever had clinical tuberculosis those who have diabetes, and those who have any evidence of cardiac disease as indicated by answers to questions six to 10 in the list given above The reasons for the refusal to use patients with a history of malaria or tuberculosis are obvious The diabetic is rejected on the justifiable grounds that as a prospective donor he will presumably refrain temporarily from eating and is, therefore, more likely to develop metabolic disturbances Of greatest importance which was not appreciated in the early days of blood bank operation is *to reject all patients who have had jaundice* (This is discussed fully on page 1165)

It is of interest to note that syncope and associated cardiovascular accidents account for the majority of undesirable incidents and complications associated with blood donation, although there is not always a causal relationship Such reactions may vary, according to Heiss and Taylor (*104*) from mild transient weakness to severe syncope A small group of individuals may exhibit a striking syndrome characterized by generalized convulsions incontinence cyanosis, and in a few cases tetany with carpo pedal spasm In my opinion, these are probably on the basis of over ventilation with the elimination of excessive amounts of

This rapid rate of formation of hemoglobin is apparently not true however when the regeneration of hemoglobin is at higher levels Fowler and Barer (*107*) found for example that the daily regeneration of hemoglobin in men was 0 049 milligram per 100 cc and in women the increase was 0 040 milligram per day following blood donations In both sexes therefore the rate of regeneration is apparently less than 0.5 per cent daily These same observers noted that the average drop in blood hemoglobin after the removal of 555 cc. of blood was 2 3 grams or a decrease of approximately 15 per cent They also made the interesting observation that the administration of 1 0 gram of iron and ammonium citrate per day augmented the daily hemoglobin increase by almost 50 per cent and shortened the recovery period from about 50 days to 35 days The possibility of administering a more suitable iron preparation such as ferrous sulfate, in doses of 0 3 gram (5 grains) three times daily, should be considered in blood donors particularly in women in order to insure the prompt return of blood to normal *Although an interval between blood donations of 56 days which is now required, appears to be a reasonable one it still is wise to secure a reliable hemoglobin estimation in the case of every person before each donation of blood is removed*

A study of 100 male professional donors in New York City has indicated that despite repeated blood donations with a required interval of rest of one week for each 100 cc of blood given not one of the donors have shown a significant failure to regenerate his hemoglobin at the end of the rest interval Even after a period of years during which time many blood donations have been given there has been little variation from the original hemoglobin reading (*108*)

It is my opinion that in a certain relatively small group of women especially between the ages of 25 and 45 years there is a tendency for anemia to develop if too many donations of 500 cc each are given For example one of my patients, a woman of 38 years, was seen with the chief complaint of ease of fatigue She was found to have a hemoglobin of 60 per cent (9 4 grams) On careful questioning it was established that she had some menorrhagia and metrorrhagia for many months and furthermore, that she had given four donations to the Red Cross at the prescribed interval of 8 weeks. There can be no question but what the removal of a total of 2000 cc. of blood in the course of eight months had augmented the anemia of which the primary cause was the excessive loss of blood from the uterus

A study of low hemoglobin levels in women as revealed by blood donor records has been made by Hervey McIntire and Watson (*109*) They found that in women between the ages of 18 and 59 years, 12 [illegible] per cent as compared to less than 1 per cent of the men were unable to meet a minimum requirement of 12 3 grams of hemoglobin per 100 cc. of blood A further study of 6911 women who had been successful donors on

of 9 98 per cent in men and one of 29 44 per cent in women The greatest causes for rejection for any single condition were recent colds in men (26 46 per cent), and anemia (59 5 per cent) in women All donors were required to have a hemoglobin level of 12 3 grams per 100 cc of blood or more as determined by the copper sulfate method, before acceptance

Fasting Condition of the Donors—It is more satisfactory to have the donor refrain from eating a heavy meal within three to five hours before blood is removed This is especially true in the case of blood which is obtained for the purposes of processing into plasma In some cases following a heavy meal with the ingestion of a considerable amount of fat there is a lipemic plasma which is undesirable It is also possible that allergic reactions are less likely to occur when blood is taken from fasting donors (In our own blood bank, however, no rules in connection with the fasting of donors have been complied with since it has been established This is because most of our donors come from out of the city and are available for only a short period of time during the day when the blood must be taken I have not observed any particular ill effects from this practice although the blood thus obtained has been utilized almost entirely as stored whole blood rather than plasma)

The Use of Blood for Transfusion Purposes Derived from Patients who Have Had Therapeutic Phlebotomies—Often the question is asked concerning the advisability of utilizing blood which has been removed from a patient for therapeutic purposes (Examples of this would be phlebotomy for hypertension congestive heart failure polycythemia vera, or polycythemia of the secondary type as seen in congenital heart disease) In general my opinion is that such blood should not be employed for transfusion purposes although there is not the slightest proof that it is injurious and undoubtedly it has been utilized in many instances Nevertheless although there is no evidence that it is harmful, some complication might occur following the use of such blood Although merely coincidental it might be claimed by the patient or the relatives that the use of such blood was detrimental, basing the claim solely on the sequence of events My advice concerning this question therefore is to use the blood of healthy adult donors only, in which every reasonable precaution has been taken to rule out disease

The Regeneration of Hemoglobin in Donors—The regulations of the American Red Cross state that a donor should not serve more often than every eight weeks or more than five times in a 12 month period This appears to be a reasonable practice and one which is ordinarily a safe one (Theoretically a healthy person with an iron deficiency anemia should regenerate hemoglobin at the rate of approximately 1 per cent per day On this basis alone an eight week interval therefore should permit the blood to increase in hemoglobin content by 56 per cent if this magnitude of increase were necessary to reach the limits of normal

been written by Cantrell and Rwitch (*111*) The following diseases have been reported as having been transmitted from donor to recipient by this means syphilis malaria homologous serum jaundice measles small pox typhus influenza tuberculosis relapsing fever encephalitis following chicken pox gonorrheal arthritis and B *suipestifer septicemia*

The fact that a person develops a disease following a blood or plasma transfusion cannot always be accepted as positive proof that the disorder has been transmitted by one or the other of these therapeutic procedures On the other hand such a sequence of events constitutes presumptive evidence which cannot be disregarded particularly if the incubation period is correct and if it occurs in more than one person It should be emphasized however that in most instances even a cursory history and examination of the donor should eliminate one capable of transmitting a disease to a recipient by this means

Although it is known that a number of diseases can be transmitted from donor to recipient some of them are obvious rare and hence of no great consequence There are three however which are of importance and should always be given serious consideration as long as blood and plasma transfusions are used as therapeutic measures they are syphilis malaria and homologous serum jaundice

The Transmission of Syphilis by Blood Transfusions—This problem is one of importance which require that every precaution be taken to prevent the transmission of this disease by this means In almost 30 years I have had three personal experiences with patients in which syphilis has been thus acquired beyond the slightest question of a doubt In one instance I refused to utilize a donor because his Wassermann reaction was found to be positive It was later discovered that this young man had served as a donor some months before at another hospital and later the recipient was observed to develop syphilis In this instance at the time of the previous transfusion a Wassermann reaction was not secured because the recipient was bleeding profusely and it was not thought advisable to delay the blood transfusion long enough to obtain this information This was almost 25 years ago and at the present time such difficulty is not likely to occur This is because with the various flocculation tests for syphilis the result can be obtained within 30 minutes Furthermore if there is any doubt about the patient s condition a plasma transfusion can be given In institutions where blood banks are established any amount of carefully tested blood is available for use at all times and hence there is no reason for a delay

A second patient a 60 year old married woman of excellent moral and social standing was admitted on my service a few years ago and much to my surprise was found to have a definite macular rash of secondary syphilis Moreover her husband s Kahn reaction was negative It was discovered that she had received a blood transfusion some weeks before

first visits revealed that 12 3 per cent had been rejected on second visits made within a year thereafter

Cases like this will occur occasionally in women of this type, but their relative infrequency does not justify the rejection of all women of this age routinely as donors by any means The establishment of a more accurate method of estimating the hemoglobin than the Tallquist which was previously employed undoubtedly eliminated some of the donors who developed an anemia, but not all In the patient's case above, it may have been that with the Tallquist scale the hemoglobin may have given an inaccurate reading which was the lower limit of normal (80 per cent) whereas a determination with a more satisfactory method of hemoglobin estimation would have indicated a definite anemia On the other hand one cannot be sure that this would have been the case For example, with the photoelectric colorimeter technic of hemoglobin estimation the reading just before the last donation might have been 78 per cent which is the lower limit of normal with our standards With the removal of 500 cc more of blood, plus the excessive menstrual loss, there may have been a sufficient quantity of blood removed from the body to account for the fall of the hemoglobin to a level of 60 per cent

The literature dealing with the immediate removal of 500 cc of blood has been reviewed by Litwins, Sussman, and Feltenstein (*110*) and the results of their own observations reported The determinations following the bloodletting were as follows, erythrocyte count hemoglobin (per cent) leukocyte count, hematocrit reading total protein (grams) albumin (grams), prothrombin time (per cent) They concluded that the removal of 500 cc of blood from healthy adult donors produced no immediate chemical or hematological alterations and that this volume of blood represents a safe and convenient amount to be used for transfusions It should be emphasized that they were concerned only with the immediate effects of phlebotomy on the hemoglobin and morphological elements of the circulating blood

Level of the Hemoglobin at Which a Blood Donation Is Permissible — From a careful study of the normal hemoglobin levels in the United States and based on my own experience (see pages 3 and 4) I would place the normal lower limit of the hemoglobin of the circulating blood for women at 12 2 grams per 100 cc (78 per cent) and 13 4 grams per 100 cc (86 per cent) for males *The criterion therefore that the hemoglobin level for donors must be at least 13 3 grams per 100 cc gives a desirable margin of safety for women, and is appropriate for men*

The Transmission of Disease by Transfusion of Blood and Plasma — With the rapid increase in the use of blood and plasma transfusions the possibility that the recipient may acquire certain disease states by this mode of transmission should be given serious consideration A review with an extensive bibliography dealing with this phase of transfusions has

been written by Cantrell and Rawitch (111). The following diseases have been reported as having been transmitted from donor to recipient by this means: syphilis, malaria, homologous serum jaundice, measles, small pox, typhus, influenza, tuberculosis, relapsing fever, encephalitis following chicken pox, gonorrheal arthritis, and B. *suipestifer septicemia*.

The fact that a person develops a disease following a blood or plasma transfusion cannot always be accepted as positive proof that the disorder has been transmitted by one or the other of these therapeutic procedures. On the other hand, such a sequence of events constitutes presumptive evidence which cannot be disregarded, particularly if the incubation period is correct and if it occurs in more than one person. It should be emphasized, however, that in most instances even a cursory history and examination of the donor should eliminate one capable of transmitting a disease to a recipient by this means.

Although it is known that a number of diseases can be transmitted from donor to recipient, some of them are obvious rare and hence of no great consequence. There are three, however, which are of importance and should always be given serious consideration as long as blood and plasma transfusions are used as therapeutic measures; they are syphilis, malaria and homologous serum jaundice.

The Transmission of Syphilis by Blood Transfusions.—This problem is one of importance which require that every precaution be taken to prevent the transmission of this disease by this means. In almost 30 years I have had three personal experiences with patients in which syphilis has been thus acquired beyond the slightest question of a doubt. In one instance I refused to utilize a donor because his Wassermann reaction was found to be positive. It was later discovered that this young man had served as a donor some months before at another hospital and later the recipient was observed to develop syphilis. In this instance at the time of the previous transfusion a Wassermann reaction was not secured because the recipient was bleeding profusely and it was not thought advisable to delay the blood transfusion long enough to obtain this information. This was almost 25 years ago and at the present time such difficulty is not likely to occur. This is because with the various flocculation tests for syphilis the result can be obtained within 30 minutes. Furthermore, if there is any doubt about the patient's condition, a plasma transfusion can be given. In institutions where blood banks are established any amount of carefully tested blood is available for use at all times and hence there is no reason for a delay.

A second patient, a 60 year old married woman of excellent moral and social standing was admitted on my service a few years ago and much to my surprise was found to have a definite macular rash of secondary syphilis. Moreover, her husband's Kahn reaction was negative. It was discovered that she had received a blood transfusion some weeks before

at another hospital As the donor was her son *it was not thought necessary to secure a test for syphilis on his blood Later I discovered that his blood Kahn reaction was positive* It is surprising to learn that some hospitals still follow the policy that if the donor is a relative a test for syphilis is unnecessary It is difficult to understand why some hospital administrative authorities can be guilty of such inexcusable gullibility

A third patient a prominent man in the community, with whom I came in contact was operated upon for cancer of the rectum This was before blood banks came into existence After the operation evidences of shock supervened which made necessary an emergency blood transfusion Blood was taken promptly from the donor for the Kahn reaction and sent to the laboratory for this purpose which in an emergency requires about 30 minutes Through an error however the blood was given to the recipient before the report of a positive reaction was noted It made no practical difference because, in this instance the patient succumbed after the transfusion of syphilitic blood had been given

It is clear from my experiences and those of many others that the transmission of syphilis by means of a blood transfusion is a possibility which must be taken into account although it occurs very rarely All donors should be asked if they had any disease including syphilis and serological reactions for this disease should be done on all donors routinely A donor should never serve even in an emergency, without the knowledge that the blood test for syphilis is negative In such emergencies previously tested bank blood or serum can be utilized and if fresh blood is used a rapid serological test for syphilis should be done prior to its injection

It is recognized of course that the statement of a patient to the effect that he or she has not had syphilis is not necessarily conclusive evidence that the person is free from the disease In some instances this is because *the patient may be guilty of concealing the true facts, and in others the* evidence of the disease may not have been apparent to the individual An indication that this is true is shown by the experience of the American Red Cross It is stated by Heiss and Taylor *(104)* that in the first 9693 Red Cross donors 24 positive blood reactions for syphilis were obtained Not one of these individuals however admitted previous knowledge of the condition although every donor in the group was questioned as to the possibility prior to the donation

In my opinion another obvious explanation should be considered concerning the positive reactions for syphilis in these persons This is the fact that some of the donors might have been recovering from mild attacks of infectious mononucleosis in this disease it is known that 10 per cent of the patients have a pseudopositive serological reaction for syphilis In one such instance the prospective bride of one of my personal acquaintances was threatened with having to postpone the

marriage ceremony because the Kahn reaction required by state law was positive temporarily as a result of this disease

According to the findings of Heiss and Taylor (*104*) the incidence of serological positive bleedings obtained in over two and one half years based on 4 million blood donations to the Red Cross was about 0 3 per cent Such a low rate is not surprising when it is considered that a person who knows that he has syphilis is not likely to present himself for the purpose of donating blood Furthermore about 40 per cent of the donations are from persons who have previously served in this capacity It is consoling to know that in the preparation of desiccated plasma and albumin the spirochaetes are destroyed and hence it is unlikely that syphilis will ever be transmitted by this means This has been shown by Turner and Diseker (*112*) who found that the organisms will not withstand the preliminary refrigeration and subsequent drying and freezing process through which all of the plasma must go

Thus the possibility of transmission of syphilis in blood banks and when whole citrated blood is employed must be kept in mind It is exceedingly unlikely that the disease will be transmitted in this way but it is possible even though the donors are questioned about the presence of such an infection and the serological reactions for the disease are negative This might occur in persons who were in the prechancre stage of syphilis for there is evidence to show that the blood at this time is infectious For example it is reported by Frazier and Pian (113) that in one patient the blood stream was invaded by the Treponema pallidum at least 20 days before the appearance of the chancre and in addition the proof of syphilis was complete in that the living organism of syphilis was isolated from the blood of the recipient by animal inoculation Hence it is possible for an individual who is unaware that he has syphilis to transmit the disease through the medium of a blood donation regardless of the fact that the serological tests for syphilis are negative

As previously stated in the case of desiccated plasma and albumin there is the additional safeguard that the processing of the material will kill the organism There is evidence to indicate furthermore that storage of blood at 4 degrees C controls the infectivity of the organisms of syphilis For example at the Johns Hopkins Hospital prior to the organization of the blood bank there were twelve cases of syphilis acquired through blood transfusions Since 1939 however there have been over 40 000 blood and plasma transfusions and not a single case of syphilis has been recognized in the recipients In 1941 it was demonstrated by Turner and Diseker (*112*) and by Bloch (*114*) that whole blood inoculated with treponemes loses its ability to cause syphilis before 96 hours of storage at 4° C and in 1942 it was shown that freezing for 48 hours likewise caused a loss of infectivity of plasma inoculated with active organisms of the disease

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The prevention of malaria due to blood transfusions is not easy. Donors should be questioned in regard to infection with this parasite. This will eliminate some infected donors but it will not control completely the hazard of transmitting malaria. It has been shown by Ackermann and Filatov (120) that tertian malaria did not survive more than 96 hours under conditions similar to those in blood banks. This is supported by clinical experience according to Cantrell and Ravitch (111) as none of the reported cases of tertian malaria infection had been transfused with blood which had been stored for as long as four days. This is not true however of the other forms of malaria as cases have been reported when transfused with blood which has been stored for as long as five to eight days. It does not seem advisable therefore to depend on blood bank storage alone to prevent inoculation with the malarial parasites.

It has been shown by Lozner and Newhouser (121) that plasma prepared from blood infected with the active quartan or falciparum parasite could be given safely after it had been stored at −20 degrees C for five to 34 days. It is of interest to note that while storage at −20 degrees C will kill the parasites freezing it at −20 degrees C will not cause the parasites to lose their virulence (122).

At the present time there are no preventive measures which can permit the use of fresh blood inoculated with malaria, for transfusion purposes. Furthermore although storage will probably render blood inoculated with tertian malaria safe for use it does not apply to blood infected with other types of malaria parasites. The only safe rule to follow is to reject as donors all persons who give a history of malaria or exposure to the disease. While this will cause the elimination of some donors unnecessarily it is nevertheless the only safe policy to accept.

The Transmission of Serum Homologous Jaundice by Blood and Plasma Transfusions.—Undoubtedly at present the greatest hazard as far as the transmission of disease by transfusions is concerned, is the risk of the recipient's acquiring serum homologous jaundice. This disorder is transmitted by a virus which is present in the plasma of the donor, and results in the appearance of the disease in the recipient after an incubation period which is usually between 55 and 135 days after the inoculation but the range is from 40 to 180 days (123).

A recapitulation of the information relative to this virus is given in an article by Runyan Wright and Beebe (124). The etiologic agent is a filterable virus which is resistant to heating at 56 degrees C in a dried condition for one half hour. It can be stored in the dried state for months is viable after being frozen for at least three and one half years and is not destroyed by being exposed to an 0.5 per cent equal mixture of phenol and ether and other bactericidal agents. The disease cannot be induced in animals but is transmitted to human beings by doses as small as 0.01 cc and probably smaller when given intradermally subcutaneously intra

The Transmission of Malaria.—Several years ago my attention was directed to the case of a patient who developed chills and fever about two weeks following a thoracoplasty. In the opinion of the chest surgeon there was no reason why such symptoms should be present from his standpoint. In the course of a routine examination of the patient's blood it was found that many organisms of malaria were present. In investigating all possible sources of infection none were considered to be likely except transmission of the condition through the medium of blood transfusions of which the patient had received a number. The diagnosis of malaria was obvious but it was not possible to prove that any of the donors to the blood bank had suffered with this disease. It is apparent, however, that such infection in donors may be exceedingly difficult to trace under these conditions, as a person may be a carrier of the disease without having active manifestations of the condition. Such an example serves as a warning that with the possibly greater incidence of malaria within the confines of the United States as a result of the returning war veterans the possibility of transmitting the disease by means of blood transfusions should be kept in mind and every precaution taken to prevent it.

According to Gupta (*115*) the first authentic report of accidental transmission of malaria through the transfusion of blood was probably made by Woosley in 1911 (*116*). He reported the transference of quartan malaria through blood transfusion in the case of a patient with pernicious anemia. Accidental induction of malaria through the intramuscular injection of whole blood has been reported by Wright in 1938 (*117*) and Nabarro and Edward in 1939 (*118*). Numerous cases are on record of accidental inoculation of malaria in narcotic addicts through the use of hypodermic syringes which are used indiscriminately for intravenous or subcutaneous injections with little or no cleaning.

The case of a patient who developed malignant tertian malaria on the fifth day after transfusion is reported by Gupta (*115*). This is the shortest period in which the malarial parasites have been known to develop in the recipient after the transfusion. The patient recovered following quinine treatment. The donor also developed malignant tertian malaria on the day following the donation of blood from which he recovered following quinine. Pending the introduction of more suitable measures for the prevention of transmission of malaria through the transfusion of blood Gupta suggests that in regions where malaria is prevalent 5 grams of quinine should be given three times a day for three consecutive days to any adult receiving a transfusion of blood.

Recently McClure and Lam (*119*) have reported two cases of malaria which resulted from the transfusion of blood stored in a refrigerator. It is of interest to note that the donors were Sicilians who had not recognized the symptoms of malaria for 25 years. *Such experiences should serve as a warning against the use of blood for transfusion purposes when collected from military personnel who have been in a malaria infested area.*

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muscularly and intravenously It is said to have been transmitted at least once by the feeding serum (*125*) and by intranasal instillation (*126*) The virus can be destroyed by exposing syringes to dry heat for one hour at 160 degrees C

Although the condition resembles infectious hepatitis and the pathological changes are identical the disease differs because homologous serum jaundice is almost always if not always transmitted by a needle injection whereas infectious hepatitis is acquired orally from ingested material contaminated by feces from a patient with the disease Most important of all is the recognized fact that cross immunity does not exist between the two conditions That is an attack of infectious hepatitis does not protect against homologous serum jaundice and vice versa although if the person has the disease due to either virus there is protection acquired against a recurrence of the same disease

The condition is a real hazard associated with transfusion of whole blood and liquid or dried plasma This is because (1) the virus is present in the blood of a prospective donor before the jaundice appears and it remains in the blood for several months and probably longer after the acute condition has subsided (2) the use of pooled plasma results in the administration of contaminated material to an increased number of individuals and (3) although ultraviolet radiation and treatment of the blood or plasma with nitrogen mustard is said to destroy the virus there is always the risk that complete destruction has not occurred Finally it is emphasized by Allen and his associates (*127*) that Lyophilization freezing and refrigeration which are the best means of preserving virus activity are also widely employed for the storage of human plasma In the opinion of these investigators if plasma is kept in the liquid state at room temperature varying from 78 to 96 degrees F the virus is apparently less likely to survive Under these conditions some of the plasma will suffer from bacterial contamination but they state that this is obviously apparent from physical changes Their data suggest that pooled plasma stored in this way is a simple and safe method for reducing or abolishing the incidence of homologous serum jaundice On the other hand as the plasma is an ideal medium for the growth of organisms it appears to me that some hazard exists from this source which may be a serious risk to the recipient and still does not give warning by producing physical changes

With the increase in the use of blood transfusions and plasma especially if pooled plasma is employed it is anticipated that there will be an increase in the number of cases of homologous serum jaundice unless highly efficient preventive measures are discovered According to the figures cited by Bunyan *et al* (*124*) there is an incidence of 1 6 to 7 3 per cent (*128*) of this disease and a mortality rate which is considerably higher than 0 2 to 0 4 per cent Hence if these figures are correct this

complication resulting from blood and plasma transfusions presents a serious problem. These figures appear to be unduly high to me although Brightman and Korns (*129*) found an incidence of 4.5 of homologous serum jaundice in a follow up of 649 patients who received transfusions of surplus Armed Forces plasma following its release for civilian use in 1945. In the operation of our blood bank for an interval of 14 years in which whole blood transfusions chiefly have been given and all patients who have ever been jaundiced have not been accepted as donors the incidence of homologous serum jaundice has been almost nil.

TRANSFUSION REACTIONS

Transfusion reactions may be classified according to the following arrangement which divides all types into two main groups namely those due to hemolysis rarest but more serious and those of a non hemolytic nature which are more commonly encountered but are usually of a less important nature.

I. HEMOLYTIC REACTIONS
   - a. Accidental use of incompatible main blood groups (O, A, B and AB)
   - b. Due to incompatibilities in the Rh system
   - c. Due to other red blood cell incompatibilities resulting from storage of erythrocytes too long

II. NON HEMOLYTIC REACTIONS
   - a. Pyrogenic
   - b. Allergic
   - c. From sodium citrate
   - d. Due to an unidentified component of plasma
   - e. Circulatory overload
   - f. Grossly contaminated blood
   - g. Embolic

The Incidence of Reactions Following Blood Transfusions.—It is difficult to estimate precisely the incidence of reactions following blood transfusions. This is because (1) often patients are not observed carefully for fever and relatively small rises may escape unnoticed, (2) not infrequently the most serious examples of a reaction are not reported in the literature, and (3) because sometimes untoward symptoms which occur following a blood transfusion are erroneously attributed to it and the reverse of this may also be true.

Certainly my earliest experiences with blood transfusion leave an unpleasant recollection of a high frequency of febrile reactions which in my opinion were pyrogenic in nature and associated with the speed at which the blood was administered often at the rate of 500 cc in one half

hour or less At the Peter Bent Brigham Hospital Boston when I was an intern in 1917 the Landsteiner technic of typing was used and the blood was given immediately after being drawn into citrate solution to prevent clotting According to a report by Drinker and Brittingham (*130*) who made a study of the reactions in this institution there was a rise of body temperature of 2 5 degrees (F) or more following 60 per cent of the blood transfusions and *a chill was associated with about one half of the febrile rises* The authors make the following statement which appears almost unbelievable at the present time we should count ourselves fortunate could we reduce reactions from transfusions of whole citrated blood *to 45 per cent*

At the present time I would estimate that when all types and degrees of transfusion reactions are taken into account the rate is about 5 0 per cent in the average hospital where all of the usual precautions are taken to prevent them Certainly if the reaction rate rises above 5 per cent a careful study should be made immediately to ascertain and eliminate the causes of such a high frequency According to Klendshoj and Witebsky (*131*) the incidence of reactions in a large series of patients at the Buffalo General Hospital was 5 5 per cent classified as follows pyrogenic 3 92 per cent hemolytic 0 18 per cent allergic 1 37 per cent circulatory 0 05 per cent and other types 0 03 per cent

There does not seem to be any evidence that reactions occur any more frequently from the use of bank blood than fresh citrated blood De Gowin and Hardin (*132*) state that the incidence of all types of reactions is no greater from transfusions of preserved blood than when fresh blood is used provided the proper care is taken in preparing and handling it The limits of storage as set by them were arbitrarily placed at 10 days for citrated blood and 30 days for the dextrose citrate mixture At the University of Iowa blood bank 80 per cent of the preserved blood is used within the first 11 days of storage (*133*) Diggs and Keith (*134*) report an incidence of 6 7 per cent reactions of all types in their series of 1415 stored blood transfusions The more serious reactions fortunately are the least common as indicated by the observations of DeGowin and Hardin (*132*) who found that hemoglobinuria occurred in 5 or 0 23 per cent and death occurred in 2 or 0 09 per cent in a large series of blood transfusions using preserved blood

A study of the reactions to transfusions with banked blood is reported by Carlson (*135*) in which the untoward results following 3388 such blood transfusions over a two year period are given He states that in the literature such reactions are said to occur following the use of stored blood in from 2 to 20 per cent of the number of transfusions given the majority of the figures ranging from 5 to 12 per cent In his own experience they were observed in 6 per cent of the transfusions and of these 11 or 0 32 per cent were considered to be of a serious nature These included three

hemolytic reactions three cases of jaundice without other evidence of hemolytic reactions two anaphylactic reactions and three cases in which cardiovascular embarrassment was caused by transfusion Death occurred in one patient who developed hemoglobinuria oliguria and repeated convulsions which were obviously manifestations of a severe hemolytic reaction This occurred despite the fact that by ordinary agglutination methods there was no incompatibility of the blood demonstrated before or after the reaction Barton (136) states that in 1022 blood transfusions with stored blood there were reactions in 6 4 per cent of the patients These were classified as follows (a) mild febrile reactions (99 to 101 degrees F) lasting but a short time following transfusions with or without evidence of hemolysis and (b) hemolytic reactions with chills and possibly hemoglobinuria and jaundice According to this observer no deaths have occurred as a result of the transfusion of blood in the operation of the blood bank at the Massachusetts Memorial Hospital since its establishment in 1938

The Blood Groups —Since the epoch making work of Karl Landsteiner and his pupils in 1900 and 1901 in which the red blood cells of humans were grouped for the first time into four types the safety of transfusing the blood of one person into another has been assured except in a small number of instances which will be noted later The fact that the blood of all persons can be divided into four main types depends upon two or they can be absent If the absence of these isoagglutinable substances or agglutinogens which have been designated by the letters A and B These characteristics in the erythrocytes may be present singly or together or they can be absent If the absence of these isoagglutinable substances is designated as O then there are four possibilities namely groups O A B and AB

When group O corpuscles are present in the blood of a person they are of the type which are not agglutinated by either the *agglutinins* A or B and therefore they can be introduced into the blood of any person without being agglutinated then hemolyzed and hence destroyed For this reason persons having red blood cells of this type are called universal donors" It should be noted however that the agglutinins A and B are present in the serum of a person with group O corpuscles and therefore such a serum will agglutinate the red blood cells of all persons except those who have the O groups namely groups A B and AB The fact that persons with group O blood may be used as universal donors is due to the fact that the red blood cells of the recipient are not agglutinated to any extent by the donor s plasma This is because although the donor s plasma contains substances which are capable of agglutinating the red blood cells of groups A B and AB it is introduced into the circulation of the recipient slowly and hence usually becomes diluted to a point where the agglutinins are no longer of sufficient titer to cause clumping and hemolysis of the recipient s red blood cells

A patient with group A corpuscles has anti B serum, and one with B corpuscles has anti A serum whereas a person with group AB red blood cells does not have either anti A or B serum

From the practical standpoint of transfusing blood into a patient the essential information to obtain is that the red blood cells of the donor will not be destroyed by the serum of the recipient This would not only nullify the purpose of the blood transfusion by destroying all of the transfused cells but would result in a severe reaction which is known to terminate fatally in about one half of the cases when 500 cc or more of incompatible blood has been given It is not so important to determine if the serum of the donor will agglutinate the red blood cells of the recipient for, as has been previously stated the donor's serum is so diluted by that of the recipient that destruction of the recipient's cells usually does not occur to an important extent *If the titer of the serum of a group O donor is above 1–32 it is thought unwise by some to employ the group O donor indiscriminately* because agglutination of the recipient's cells may occur to a degree which is dangerous A further discussion of the inadvisability of employing blood from a so called universal donor will be given later

The Incidence of the Various Blood Groups—The following table gives the incidence of the four main blood groups as shown by data collected by various observers

Blood Group	*Schiff & Boyd (137) %*	*Snyder (138) %*	*Barton (136) %*
O	40	45	45
AB	5	4	4
A	40	41	39
B	10–15	10	12

The following table shows the presence of the various agglutinins in the serum

Red Blood Cell Group	*Agglutinins in the Serum*
O	anti A and B
A	anti B
B	anti A
AB	none

Use of this information is made in the typing of unknown red blood cells by using anti A and anti B typing sera If the unknown red blood cells are agglutinated by anti A they are type A if they are agglutinated by anti B they are B if they are not agglutinated by either they are type O and if they are agglutinated by both they are type AB *Regardless of the results of the tests for determining the blood types all donor blood must be cross matched with the blood of the recipient as a check to prevent errors before being used for a blood transfusion*

Although four main types of human blood are now recognized which are distinguishable serologically there are many sub groups which greatly increase the number For example there are eight classes of the A B system five classes of the M N system two classes of the P system and the five types of Rh agglutinogens (*139*) Hence there would be theoretically at least 400 different kinds of human blood which could be distinguished by *serological reactions* This is indicated by multiplying the figures given above namely $8 \times 5 \times 2 \times 5 = 400$

It is of interest to note that over 30 antigens have been detected in the erythrocytes of cattle by means of isoimmune sera produced by transfusing blood from one animal to another or by immunization of rabbits with bovine cells or by both methods (*140*) Since these antigens are passed directly from the parents to the offspring these characters may be used for exclusion in cases of disputed parentage of cattle With the recent discovery of the Rh blood types the chances of excluding parentage in humans are raised from 33 to almost 45 per cent

Nomenclature of the Blood Groups—The original nomenclature introduced by Landsteiner (*141*) and his pupils DeCastello and Sturli (*142*) designated all red blood cells as being of four groups namely A B AB or O Following this Jansky (*143*) and later Moss (*144*), introduced numbers instead of the letters originally used and unfortunately caused unnecessary confusion In order to keep the nomenclature correct in one s mind a comparison of the different designations is given below

Landsteiner	*Jansky*	*Moss*
O	I	IV
A	II	II
B	III	III
AB	IV	I

For the test sera the official designation should be test serum A (anti B) and test serum B (anti A)

The blood group system has become so expanded since 1901 that now it is a most complex subject whose ramifications can only be mastered by skilled specialized serologists The A B O system has been subdivided so that group A has a number of divisions designated as A_1 A A_3 According to Andresen (*145*) only A_1 and A are of importance and hence the extended A B O system includes six groups as follows O A_1 A B A_1B and A B When the M N system is also included this makes a total of 18 blood groups

From a practical standpoint the introduction of the A B O system by Landsteiner and his associates was monumental in importance The addition and recognition of the Rh groups by Landsteiner and Wiener in 1940 (*146*) was a great step in advance in clinical medicine as it provided a basis for the etiology of erythroblastosis fetalis and also

explained certain hemolytic reactions of a previously obscure nature. The M and N agglutinogens and factor P are rarely of importance insofar as the cause for hemolytic reactions in recipients is concerned but they have been reported as responsible for this (*147, 148*).

It is consoling to read the statement by Race and Sanger (*149*) who say apropos of the many Rh types "For clinical purposes we think that physicians, surgeons and obstetricians should not be bothered with more than Rh positive, Rh negative and anti Rh at present and when fathers of children with haemolytic disease are being reported on, Rh positive homozygous or Rh positive heterozygous with the insertion of the word probably when appropriate." For a recapitulation of information concerning the importance of the special groups such as A_1A_2, MN, MNS, P, Rh, Lutheran, Kell, Lewis, the secretion phenomena, the Duffy group and others the reader is referred to the excellent monographs by Race and Sanger and by Andresen previously mentioned.

Hemolytic Reactions.—A reaction of this nature may be defined as one in which either the erythrocytes of the donor's blood are hemolyzed by the recipient's serum or the donor's serum has a similar effect on the recipient's cells. The former situation is the one of importance as rarely does the donor's blood contain a sufficiently high titer to cause agglutination of the recipient's cells. This may happen, however, when group "O" is employed as a universal donor and occasionally give rise to serious reactions of a hemolytic nature (see page 1186). Occasionally hemolytic reactions may be due to cold agglutinins or when there is iso immunization to blood factors other than A, B or the Rh group in the blood of the recipient. Furthermore, increased rate of destruction of erythrocytes may occur when the transfused blood has been stored an undue length of time and for that reason preserved blood which has been kept under ideal conditions for longer than 30 days should not be used. It is sometimes difficult to transfuse patients with an acquired hemolytic anemia due to agglutination of the erythrocytes in vivo by the recipient when this has not been apparent in the cross matching tests.

The *symptoms* of a hemolytic reaction vary widely, being proportional to the extent and rate of hemolysis. It is known that the clinical manifestations arise as the result of free hemoglobin in the plasma of the recipient. If the plasma of the latter is examined within 12 hours after a severe hemolytic reaction it is likely that oxyhemoglobin will be present according to Mollison (*150*), but within 24 hours one would expect to find methemoglobin. It is known that some of this material is excreted in the urine and some joins with the plasma albumin but the greatest part is transformed to bilirubin. Hence if blood is withdrawn from a vein in a dry test tube without stasis as soon as the symptoms of a hemolytic reaction occur the plasma will be pinkish; three to six hours after the onset of hemolysis it may be a bright yellow color due to the hyperbilirubinemia

The symptoms associated with hemolytic reactions vary widely from a complete absence to those associated with severe shock anemia and death The most characteristic manifestations are burning in the vein above the site of the transfusion needle flushing of the face sharp pain in the lumbar region tachycardia occasionally chest pain and nausea and vomiting Sometimes there may be a slight chilly sensation or even pronounced rigors which are followed by a febrile rise varying from 99 2 F to 101 to 103 degrees or higher Any or all of these manifestations may be absent and the only evidence which attracts one's attention to the fact that there may have been an abnormal destruction of blood is the failure of blood transfusions to increase the hemoglobin content and red blood cell count of the circulating blood The most serious complication is anuria which occurs in a minority of patients in whom at least 200 cc of blood has been destroyed In a considerable proportion of cases, the course of events is intravascular agglutination followed by hemolysis hemoglobinemia hemoglobinuria ominous general symptoms oliguria anuria uraemia and death This serious complication will be discussed under a separate heading (see page 1177)

The Signs of Increased Intravascular Blood Destruction —According to DeGowin (*151*) the diagnosis of a hemolytic reaction can be made on the observation of the post transfusion blood plasma If it is reddish it contains over 10 milligrams of free hemoglobin per 100 cc or if it is deeper yellow than the control it may be assumed that some degree of hemolysis is present This observer also states that the presence of hemoglobin without erythrocytes in the post transfusion urine specimen is positive evidence of hemolysis

The rate of removal of free hemoglobin from the plasma depends to some extent on the concentration of this substance for the higher it is the more rapid is its removal It has been shown by Ottenberg and Fox (152) that when the initial plasma level is approximately 200 to 300 milligrams per 100 cc one half or more may be removed in as short a time as three hours although small amounts will remain for eight to 10 hours When the plasma level is only 40 to 60 milligrams per 100 cc it may be cleared in five hours

It is emphasized by Flink (153) that the majority of reactions following blood transfusions are of the simple febrile or urticarial types but some are hemolytic In studying reactions he employed a method whereby the hemoglobin of the plasma was converted to pyridine hemochromogen and measured by means of the Evelyn photoelectric colorimeter Normal values by this method are from a trace to 5 milligrams per 100 cc of plasma With free plasma hemoglobin concentrations of from 20 to 25 per cent per 100 cc the presence of hemolysis in the plasma is evident to the eye In 19 non hemolytic reactions he found that the hemoglobin in the plasma did not exceed 12 milligrams per 100 cc and in most

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tration may result from the rapid breakdown of as small amount as 60 cc of whole blood The hemoglobinuria once begun will persist until the hemoglobinemia is far below the original threshold Hence it is not uncommon to observe a hemoglobinuria for 24 hours or longer

With an alkaline urine the hemoglobin is excreted in the form of oxyhemoglobin which causes the urine to be red in color If the reaction of the urine is neutral or acid however it will have a dark brown appearance due to the formation of methemoglobin Hemoglobinuria is always accompanied by albuminuria when it follows an incompatible blood transfusion (*156*) It may also be accompanied by glycosuria as indicated by the animal experiments of Ottenberg and Thalhimer (*157*)

It is mentioned elsewhere that the most serious complication of intravascular hemolysis is some degree of renal failure which is known to be the cause of death in the fatal cases The theory that this is due to blockage of the renal tubules with acid hematin a relatively insoluble compound of hemoglobin which is formed in acid urine is no longer tenable It is now generally thought that the renal insufficiency is due to degenerative changes in the renal tubules as a result of some "nephrotoxic" factor When severe renal damage occurs there may be no signs of it for the first two or three days after the incompatible transfusion has been given for during this interval the recipient may appear to be well After this latent period however the general symptoms appear and usually between the sixth and twelfth days the patient becomes comatose and succumbs or at this time begins to void large quantities of urine and recovery follows (*158*)

The signs of increased blood destruction regardless of the mechanism are essentially the same According to Mollison (*156*) when the blood bilirubin reaches a level of 4 milligrams per 100 cc clinical jaundice is apparent It is stated by Vaughan (*159*) that although the blood bilirubin concentration reaches a peak within five to six hours after increased blood destruction obvious jaundice is not likely to occur until the end of approximately 12 hours as time is required for staining of the tissues

There are at least two other factors which may have a bearing on the intensity of the jaundice when there is increased intravascular destruction 1 The rapidity of blood destruction is important in this connection for when it is slow the increased amount of bilirubin can apparently be disposed of effectively and hence only slight or no jaundice results 2 *It is known that damage to the liver may follow the transfusion of incompatible blood* and hence a "toxic" jaundice factor may be added in some cases

Once the destruction of blood is completed the serum bilirubin concentration falls rapidly and usually reaches normal limits within two or three days It is not common for jaundice of this nature to persist for longer than two or three days

instances it was below 9 milligrams per 100 cc In studying five cases of hemolytic reactions he observed that within 48 hours oxyhemoglobin was present in the plasma and in 68 hours methemalbumin was detectable All five of his patients became jaundiced on the day following the reaction, thus substantiating the hemolytic nature of the process The hemoglobin in the plasma reached as high as 125 milligrams per 100 cc in one of the patients

It has been shown by Fairley (*154*) that the disposal of hemoglobin may be accomplished in at least three ways when it is liberated into the plasma from the erythrocytes (1) When the hemolysis is slight the hemoglobin is absorbed by the cells of the reticulo endothelial system converted to bilirubin carried by the blood stream to the liver and excreted in the bile (2) With a greater concentration of the hemoglobin

Fig 78 —A low power microphotograph illustrating the hematin granular masses obstructing the collecting tubules in a patient who suffered from a fatal hemolytic reaction following the transfusion of 400 cc of incompatible blood Within a few hours after the transfusion red urine containing hemoglobin was passed and the following morning jaundice was present The urinary output was less than 90 cc for the remaining 25 days of her life The non protein nitrogen rose to 245 milligrams per hundred cc Retyping of the blood showed that a group II donor had been utilized for a type I recipient (Goldring and Graef courtesy *Archives of Internal Medicine*)

in the plasma a part is broken down as hematin This substance combines with serum albumin to form methemalbumin a pigment with a characteristic spectroscopic picture Recognition of this material in the serum is possible within 5 hours after hemoglobin is freed in the blood and, according to Fairley it will persist for 24 hours or more (3) Some hemoglobin is excreted by the kidneys but according to Gilligan and his associates (*155*) this only occurs when the concentration in the plasma reaches 135 to 180 milligrams per 100 cc It is said that such a concen

been rapidly destroyed. Evidence of a valuable nature can be obtained by proving the presence of immune agglutinins in the recipient's serum. For a full consideration of the details of the most effective method of investigating a hemolytic transfusion reaction reference should be made to the comprehensive study of Mollison (*156*). Having determined that a hemolytic reaction has occurred the following tests should determine the cause of the reaction (1) grouping of the donors and recipients cells (2) cross matching in the A B O system (3) cross matching in the Rh Hr system (4) typing for Rh Hr and (5) considering other causes such as the recipient's having a hemolytic anemia the presence of cold agglutinins etc. Further details for carrying out such an investigation are given by DeGowin (*150 151*).

Etiology of Anuria Following Incompatible Blood Transfusions—If more than 200 cc of incompatible blood is injected into the veins of a human recipient and it is entirely hemolyzed renal damage of such a severe nature will result that death will occur in about 15 to 20 per cent of the cases. According to Muirhead and Hill (*162*) there were 17 known hemolytic reactions at the Baylor Hospital Dallas Texas in 38 917 blood transfusions which gives an incidence of 0 43 per 1000 of these three were fatal. When five additional patients who had been referred to this clinic for treatment are taken into account of whom one died there was a mortality rate of four deaths in 22 cases or 18 1 per cent.

No one will deny that anuria is the most serious complication of transfusion therapy and that such tragic incidences continue to occur occasionally. With the huge increase in the number of blood transfusions which are now given due to a better understanding of the indications and the satisfactory development of the blood bank it is remarkable that the incidence of such a complication is not higher. As long as humans occasionally err and many transfusions are given the remote risk of giving incompatible blood as a transfusion must always be faced.

The exact cause of renal failure in such patients is in dispute. Baker and Dodds (*163*) in 1925 put forth as the explanation of the renal insufficiency the liberation of hemoglobin from the red blood cells and the precipitation of this material in the renal tubules which caused a blockage in the presence of an acid urine. It was found that this was the case in rabbits to which an incompatible blood transfusion had been given. Furthermore it was discovered that when the urine was kept alkaline this did not occur. Evidence has been accumulated however to indicate that this is probably not the explanation of the renal insufficiency in humans who have hemolyzed large amounts of blood. Never has it been demonstrated in a patient who succumbed to such a transfusion reaction that a sufficient quantity of hemoglobin had been precipitated to produce uraemia. The evidence indicates that following an incompatible transfusion there is profound degeneration of the renal

The immediate symptoms which arise as the result of an incompatible transfusion are severe lumbar pain, flushing and burning of the face, a sensation of tightness and constriction in the chest, and chills with some degree of collapse. All of these symptoms may be controlled with morphine.

It is of interest to note that when an incompatible transfusion is given the majority of the donor's cells are eliminated within a few hours after they are injected into the circulation of the recipient. In some instances it is possible to find clumps of agglutinated cells in the blood sample withdrawn from the recipient, and these may persist in vivo for 24 hours. It is known that under these circumstances the agglutinins of the recipient's serum responsible for the destruction of the donor's red blood cells undergo certain characteristic changes (*160, 161*). There is usually a reduction in agglutination titer in the first two or three days following the transfusion. This phenomenon has been attributed to absorption of the agglutinins by the incompatible erythrocytes. Following this phase there is usually a rapid increase in the strength of the titer which reaches a peak in 10 to 20 days after the transfusion.

As a result of the increased blood destruction, the anticipated red blood cell and hemoglobin rise may not appear in patients to whom incompatible blood has been given. This will also occur in patients who have been transfused with blood which has been retained too long in the blood bank. The failure of a blood transfusion of 500 cc to produce a rise of approximately 300,000 to 400,000 red blood cells per cubic millimeter and an elevation in the hemoglobin of 10 per cent should arouse the suspicion that the patient has (1) either destroyed the transfused blood or (2) continued to lose blood either by hemorrhage or by increased destruction due to other causes, such as those which are active in the causation of hemolytic anemias. Additional and probably more reliable evidence of the survival or failure of survival of the transfused red blood cells may be obtained by the differential agglutination technic.

When it is suspected that a recipient has hemolyzed incompatible blood the establishment of such a possibility as a fact depends in part upon demonstrating a cause for it. These, according to Mollison (*156*), are most commonly (a) mistakes in blood grouping, (b) the use of Rh positive blood in recipients who are sensitized to the Rh agglutinogen, and (c) failure to maintain adequate standards in blood storage.

This same investigator states that when a patient is seen within 12 to 24 hours after such a transfusion the increased destruction can be demonstrated by simply obtaining a venous sample from the recipient and showing that it contains oxyhemoglobin, methemalbumin, or an increased concentration of bilirubin. If the patient is observed at a time later than this, the application of the method of differential agglutination is the only way of demonstrating that the donor's red blood cells have

pigment is the cause of anuria following crushing injuries and incompatible blood transfusions It is pointed out by the author that although the agent differs it is possible that the sequence of events consisting either of vasoconstriction or tubular destruction followed by blocking with *cellular detritus is identical Although the role which acidosis plays is* not clear it is known that its presence is required for the development of both experimental methemoglobin anuria and the clinical anuria mentioned This is indicated by the value of alkalinization therapy in blackwater fever the crush syndrome and mismatched transfusions It is suggested by Bing (*169*) that acidosis exerts its toxic influence in conjunction with methemoglobin through inhibition of respiratory enzymes present in the tubular cells although proof of this is lacking at present

The experiments of Yuile Gold and Hinds (*170*) may shed some light on this question They found that hemoglobinuria does not produce changes of importance in the normal kidneys but when renal damage has been produced by a relatively brief period of ischemia there is precipitation of hemoglobin in the renal tubules The precipitation is greater when the urine is acid In studying the changes associated with hemoglobinuric nephrosis in traumatic shock it has been observed by Mallory (*171*) that there is lipid vacuolization of the ascending limbs of Henle s loop necrosis and regenerative changes in the epithelium of the ascending limbs and distal tubules in some instances rupture of the tubules with herniation of their content and the formation of non-occlusive thrombi in many of the small veins

In summary there seems to be good evidence to indicate that hemoglobinuria by itself is not the sole cause of the renal damage which occurs in some patients who hemolyze large amounts of blood intravascularly It is likely that a number of other factors act in conjunction to produce this serious renal change which results in anuria and sometimes death of the patient from uremia The likely causes may be listed as follows (1) The amount and rate of liberation of the hemoglobin This depends on the quantity of blood which is given the rate of injection and the titer of the hemolysin (2) The previous injury to the kidney which in some instances may be on the basis of previous unrelated disease but more commonly the initial associated shock with resultant renal damage due to ischemia dehydration and possibly an acid pH of the urine Undoubtedly other unknown factors also play an important role in the production of this condition

Treatment of Acute Renal Failure with Anuria Following an Incompatible Blood Transfusion—The treatment of acute renal failure due to this cause is the same as the treatment when it is associated with any other condition If the patient is in shock then therapy should be directed toward the low blood volume which is the basis for the outstanding manifestation of the condition namely the hypotension Pro

tubules which *accounts for the clinical manifestations* The cause of the degeneration is not known

It has been shown by De Navasquez, however (*164*), that in normal animals, when the urine has been rendered acid large quantities of hemoglobin can be excreted without producing renal damage A most comprehensive review of hemoglobinuria and its effects on the kidney, with a report of his own experiments on this subject, has been published by Flink (*165*) He states among other conclusions that *when 1 0 gram of* hemoglobin or more per kilogram of body weight is injected intravenously into dogs 25 to 40 per cent is excreted by the kidneys and the remainder is destroyed in the reticulo endothelial system or in the circulating blood with the formation of bilirubin or hemosiderin He found also that *the amount of hemoglobin excreted is approximately the same when the urine is alkaline as when it is acid* He observed two important changes in the kidneys of dogs that developed renal insufficiency namely (1) a large number of hemoglobin casts in the loops of Henle and distal tubular segments with occlusion of the majority of tubules by casts with serious or fatal renal damage (2) Degenerative changes occurred in the tubular epithelium as early as four hours after the injection reaching a maximum *in five to seven days If the dogs lived longer there was a gradual* restoration of normal kidney architecture *He commented that his observations were the same as those of previous observers with the exception that dogs with alkaline urine had renal changes approximately as severe as those with an acid urine* His experiment also supported the belief that renal damage is proportional to the initial plasma concentration of hemoglobin and the average of the initial and 24 hour plasma concentrations

Of considerable importance are the observations of Mason and Mann (*166*) and of Hesse (*167*) which indicate that when hemolyzed blood is given intravenously the *renal vessels are constricted and there is transient diminution in the kidney volume These experiments indicate that renal* ischemia with *its resultant damage must be considered* as an important factor in the cause of anuria following a hemolytic blood transfusion Evidence has also been produced by Lalich (*168*) that dehydration may be responsible for precipitation of hemoglobin in the kidneys when hemoglobinuria is present

In a study of hemoglobin and related pigments on the renal function of the normal and acidotic dog Bing (*169*) states that a number of conditions have been reported in man in which the excretion of pigmented urine is followed by anuria and death In blackwater fever the urine contains methemoglobin myoglobin is excreted during crush injuries and hemoglobinuria follows both incompatible transfusions and crushing injuries Since myohemoglobin has only been demonstrated in the urine of patients suffering from blackwater fever it is doubtful whether this

Seligman and Fine (173) the use of some type of so-called artificial kidney and the employment of exchange transfusions Conclusions regarding the value of these forms of therapy cannot be formulated at present and I cannot make any statement concerning their efficacy from first hand experience

The Rh Factor in Human Blood —In a brief note in the *Proceedings of the Society for Experimental Biology and Medicine* for January 1940 Landsteiner and Wiener record for the first time information concerning the discovery of the Rh factor in human blood They found that when red blood cells from rhesus monkeys was injected into rabbits immune serum was produced which had the property of agglutinating the red blood cells of a great majority but not all of the human beings of the white race They designated this agglutinable property of human erythrocytes as the Rh factor because it was present in all of the red blood cells of the rhesus monkey and because cells from this species served as the stimulus to the formation of the agglutinin in the blood of rabbits In their brief preliminary report it was stated that these results were of some interest in that they suggested a way of finding individual properties in human blood namely with the aid of immune sera which had been developed in the blood of animals

A resumé of the main facts relating to our present knowledge concerning the Rh factor may be stated briefly as follows (a) it is an antigenic substance contained in the red blood cells of a high per cent of all humans and all rhesus monkey cells similar in some respects to other previously discovered antigenic factors such as A B M and N (b) it occurs only in the red blood cells as does the agglutinogens M and N but differing from A and B which occur in the tissues and secretions of at least some persons (c) this factor is inherited as a mendelian dominant characteristic as are the other blood group factors (d) the Rh agglutinogen occurs in about 85 per cent of white people in 92 per cent of Negroes in almost 100 per cent of the Chinese and in all Macacus rhesus monkeys (e) there are no normally occurring agglutinins against the Rh factor in man which is also the case in M and N whereas agglutinins are normally present in man against A and B occurring naturally (anti A and anti B) (f) it is known however that if red blood cells containing the Rh factor (RH+) are introduced into the circulation of a person whose red blood cells do not have the Rh factor (RH−) agglutinins (called anti Rh agglutinins) may develop against it and (g) however it is generally considered that anti M or N agglutinins are not likely to develop if blood containing the M and N factors is injected into persons without these factors in the blood that is M negative or N negative recipients Hence it can be stated that the Rh factor has iso immunizing ability whereas this is certainly not prominent in the M and N factors For this reason it is claimed by some that M and N factors have slight if any significance

vided the cause of the incompatible blood transfusion can be determined and avoided, then blood should be given intravenously with caution in order to raise the blood pressure. Care should be used by slow administration to avoid overloading the cardiovascular system. If it is thought inadvisable to give whole blood, then plasma may be utilized.

Experience has taught that such patients should not be given an excessive amount of fluid. The total amount administered in any 24 hour period should not exceed 1500 cc which includes oral as well as parenteral fluids. Furthermore diuretics are of no value and should be avoided.

In addition to the treatment of shock, if present, the main principles of therapy are concerned with maintaining the proper balance of fluid protein and electrolytes in the circulating blood. Limitation of fluids to 1500 cc per 24 hours has already been mentioned. This is all the body can excrete by the lungs, stools and sweat. To give more would be risking the possibility of causing cerebral or pulmonary edema. Protein should be restricted to 40 grams daily or less as this is about the amount the average individual breaks down in a 24 hour period. A relatively high carbohydrate and fat with low protein diet imposes a minimum amount of work on the part of the kidney in the elimination of the end products. The diet recommended by Bull, Joekes and Lowe (172), when given by a small stomach tube is satisfactory. This diet has the following composition: dextrose 400 grams, peanut oil 100 grams, acacia q s to emulsify and water to 1 liter. It is recommended that it be given by steady drip through a small stomach tube throughout the 24 hours and continued until the patient voids 1000 cc per day.

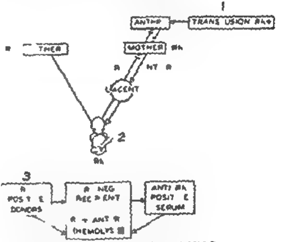
In addition to this, the following chemical determinations should be obtained on venous blood if possible: blood carbon dioxide combining power, calcium, chlorides, creatinine, non protein nitrogen, potassium, phosphorus and sodium. If any of these are found to be below normal limits then one or more of these should be administered intravenously in appropriate amounts as indicated: sodium chloride, sodium citrate, potassium bicarbonate, potassium chloride and calcium gluconate. By such therapy an attempt is made to keep the electrolyte balance within normal limits. As the kidneys in this condition have the ability to recover even after a relatively long time, it is worth while to persist in the rather complicated therapy in the hope that the patient can be carried along to the point where improved function will return.

It should be kept in mind when diuresis does occur that there may be a severe deficiency in some of the electrolytes of the circulating blood. This may require correction in order to avert serious consequences. Hence the patient at the period of apparent recovery will require careful observation in order that the proper treatment may be instituted or continued.

Other forms of therapy which have been suggested in the stage of anuria are the procedure of peritoneal irrigation as introduced by Frank

prevent hemolysis of the donor's erythrocytes under these circumstances such a patient should be transfused only with blood from a Rh negative donor

The Practical Aspects of the Rh Factor in the Blood —As previously stated the Rh factor may be responsible for serious and even fatal reactions in pregnant women in infants with erythroblastosis and in patients who receive repeated blood transfusions It should be emphasized that in addition to typing all blood for transfusions according to the ABO



THE IMPORTANCE OF THE Rh FACTOR IN BLOOD TRANSFUSIONS

Fig 79 —There are at least three important dangers which may arise as a result of the Rh factors of the blood In (1) it is shown that if Rh positive blood is transfused into a female who is or has been pregnant a hemolytic reaction may result This is because the female may have had anti Rh agglutinins formed as the results of bearing an Rh positive child The Rh positive red blood cells of the fetus in which the positive Rh characteristic has been inherited from the father stimulates the formation of anti Rh agglutinins in the mother Harm may then result from two different mechanisms (a) the mother may hemolyze Rh positive blood which is given as a transfusion and (b) the anti Rh agglutinins may pass through the placenta and hemolyze the erythrocytes of the fetus thereby causing the syndrome of erythroblastosis fetalis as indicated and (2) it should also be kept in mind as shown in (3) that if an Rh negative recipient is transfused a number of times with Rh positive blood the initial transfusions may stimulate the formation of anti Rh agglutinins and when they reach a sufficiently high titer they may destroy Rh positive erythrocytes which are injected in subsequent transfusions

system of four main groups and employing identical groups for transfusion donors *direct matching of the donor's red blood cells with the recipient's serum is necessary* When this is carried out with the Landsteiner Levine test tube technic and an incubation period of at least 30 minutes in the opinion of Dameshek (176) "this method is sufficiently sensitive for the detection of the great majority of normal and abnormal agglutinins of low titer including the Rh agglutinin"

The slide test is suitable for ordinary typing but should not be employed in cross matching as it is relatively insensitive especially for the weakly reacting types of those that react best in the incubator including the anti Rh agglutinin The additional suggestion is made by Dameshek

with respect to hemolytic reactions in blood transfusions whereas the Rh factor is of great importance in this respect For further details concerning the Rh groups the reader is referred to the comprehensive discussions by Race and Sanger (*174*) and by Andresen (*145*)

The Clinical Significance of the Rh Factor—It is now determined that the Rh factor is of importance in medicine in at least three conditions namely 1 in patients who receive repeated blood transfusions 2 in pregnant women and 3 in infants with erythroblastosis fetalis Only the first topic may be discussed here Reference should be made to Chapter XII on Erythroblastosis Fetalis page 521 for a presentation of the other aspects of the Rh factor

The Importance of the Rh Factor in Patients Who Receive Repeated Transfusions—*Soon after the Rh factor had been discovered it was* found by Wiener and Peters (*175*) that some patients when transfused *repeatedly with the proper A, B, O groups did not have untoward symp*toms until a number of transfusions had been given and then, even though *the correct group had been utilized as donors, a hemolytic reaction* occurred

I had observed such a sequence of events to occur occasionally over 20 years ago and had often pondered over the significance of it For example one of my patients with pernicious anemia who received 32 blood transfusions before liver therapy had been introduced in the treatment of the condition had a severe reaction when the same donor was used for a second time With the initial use of the blood of this donor there had been no reaction and it was at the request of the patient some time later when a number of other transfusions had been given that this individual be employed again in the hope that a reaction would not occur To my amazement a severe reaction did occur which led me then to assume that some change must have occurred in the recipient With our present knowledge it is possible the explanation of this phenomenon was associated with the development of anti Rh agglutinins At the time there did not appear to be any logical explanation of this reaction as the knowledge concerning the Rh factor was not available until some years later

The mechanism concerning severe reactions following repeated blood transfusions is now quite clear as it is known to be due to the effect of the anti Rh factor The following is the sequence of events in such a patient The recipient is one of the 15 per cent of the white population of the country who has Rh negative erythrocytes (Rh−) The initial donors are those who comprise 85 per cent of the population with Rh positive (Rh+) red blood cells These when injected as a blood transfusion act as antigens and after several transfusions stimulate the formation of anti bodies in a titer which have the capacity to agglutinate and hemolyze the donor s Rh positive red blood cells (anti Rh agglutinins) In order to

recipients (male or female) of repeated transfusions 2 for all women requiring transfusions 3 to avoid serious reactions in those who have borne an infant with erythroblastosis fetalis 4 to avoid sensitization of Rh negative women of child bearing age 5 for the listing of Rh negative donors for emergency use and 6 for the procurement of Rh negative banked blood to be given to Rh negative patients It is of *special importance* to do an anti Rh determination 1 in pregnant women whose histories show that one or more previous pregnancies ended in late stillbirths 2 infants with severe jaundice or anemia or even infants deaths apparently due to hemorrhage or anoxemia 3 in Rh negative women who have received transfusions especially from their husbands and 4 in Rh negative women married to Rh positive men who have had one or two children and may therefore be sensitized to the Rh factor

The Use of the "Universal Donor"—My own experience with the use of universal donors since 1917 has indicated to me that the practice is apparently not a dangerous one even though it is recognized that the serum of the donor will agglutinate the red blood cells of the recipient Apparently almost without exception the titer of the donor s serum is such that the dilution which occurs in the recipient s blood reduces it to a point where hemolysis of the recipient s cells does not occur

A most comprehensive review of the entire subject is presented by Rosenthal and Vogel (*179*) They state that in reviewing 11 725 blood transfusions which were given during the years 1930 to 1940 819 universal donors were used (in 6 9 per cent of the cases) In these transfusions there were 68 or 8 3 per cent of reactions which is approximately the number expected when donors of the same group are employed They conclude by stating that universal donors may be used safely in medical and surgical cases

In their experience furthermore the underlying conditions for which the transfusions are given such as anemia shock and hemorrhage are just as favorably influenced as they are with homologous blood Reactions such as chills urticaria fever and hemolysis statistically are not any greater than in the general run of transfusions In the 819 cases in which universal donor blood was employed not a single fatality occurred as the result of the transfusions

At present it is not necessary to use universal donors as commonly as it has been in the past This is because often it was not possible to find the proper group among the family and friends and the universal donor was employed to avoid the expense of a professional donor This is now obviated in most instances in large institutions by the use of the blood bank

Universal donors have also been employed in emergencies such as shock and of course they are still of use for this purpose In many

(*176*) that unless a laboratory has a highly *potent anti Rh testing* serum it is important to perform a careful compatibility test of the recipient's *serum with the prospective donor's cells* To do this the time in incubation should be prolonged to one hour It has been suggested by Boorman Dodd, and Mollison (*177*) that a modification of the Levine technic be used which they believe brings out the anti Rh agglutinin more satisfactorily They suggest that the mixture of the recipient's serum donor's red blood cells and saline solution remain in the incubator at 37 degrees C for a period of two hours The sediment is then examined with a hand lens and a *portion is pipetted off for microscopic examination If such a* test is negative the transfusion may be given with *almost* complete safety but the reservation may be with a completely negative in vitro test, there still may rarely be in vivo reaction

There is only one way to avoid absolutely the difficulty encountered with the Rh factor and that is to determine the Rh factor in both the cells of the donor and the recipient Having then determined this information *Rh negative recipients should be transfused only with Rh negative blood* Such Rh factor determinations are simple to make provided potent Rh *agglutinating serum is available* At present this can usually be obtained from centrally located laboratories In large institutions where many blood transfusions are given *all donors are typed for the Rh factor* and a list kept of those who are Rh negative These can be placed on call for emergencies In some instances it may be necessary to employ a group O Rh negative donor, if an Rh negative donor or the same main blood group is not available

In a comprehensive summary of the clinical importance of the Rh blood type Diamond (*178*) makes the following statements, which are quoted in part *The Rh blood type present in about 87 per cent of the white* population is of practical *importance almost exclusively to the persons who lack it* In the latter repeated transfusions of Rh positive blood cells may lead to increasing hemolytic reactions due to the interaction of anti Rh agglutinins initiated by the first Rh positive transfusion with specific agglutinogen of the infused cells Rh negative women married to Rh positive men may be sensitized by means of one or more pregnancies involving an Rh positive fetus the Rh factor being inherited as a dominant trait Although this only occurs in one of about 15 such matings once so immunized the woman cannot safely be given even one transfusion of untyped or Rh positive blood since it may be followed by a serious even fatal *hemolytic reaction A single Rh positive* transfusion to an Rh negative woman married to an Rh positive man may initiate the antibody response and a subsequent pregnancy *with an Rh positive fetus* may end in the severest form of erythroblastosis fetalis in the infant Women of child bearing age must therefore be protected *against* this potential danger It should be emphasized that Rh typing is necessary for all

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to 105 F within one hour His urine became dark wine in color This febrile condition continued for 36 hours The untoward reaction was attributed to the high titer of the group O donor s serum which was found to be 1 320 The author regards this case as an instance of a proven "dangerous universal donor" A severe hemolytic reaction is reported by Ervin and Young (169) which occurred in a group A recipient following a transfusion with group O blood having an unusually high titer of A antibodies

In this connection it is of interest to note the work of Thalhimer (190) who has demonstrated that in pools of a sufficient number of samples of plasma or serum obtained from donors belonging to all four groups the titer of both anti A and anti B agglutinins is reduced to such a low level that no danger can result to patients from the injection intravenously of even large therapeutic doses of these pools

An interesting suggestion has been made by Litwins (191) that the combination of O cells with pooled plasma constitutes an ideal and safer and economical medium of universal blood The plasma from all four groups is diluted and hence is safer than the indiscriminate use of ordinary universal O blood Obviously this procedure applies only to institutions with blood banks and does not seem necessary in view of the present general belief that universal donors can be used with safety when other donors of the same type of blood as the recipient are not available

Embolic Reactions —Although for many years it was my custom to take refuge in the thought that anything which would pass through the average 19 gauge needle would do no particular harm to the patient receiving an intravenous injection this is not entirely true Regardless of my consoling thought it was always my practice to filter the citrated blood immediately before it was given When preserved plasma and serum are used they likewise should be filtered properly for at least one death has been reported (192) from multiple fibrin emboli following a transfusion with citrated plasma With the modern methods of collecting blood and citrating it promptly and efficiently and with the use of the filter which is included in all modern apparatus for injecting blood embolic phenomena should rarely if ever be encountered

Reactions Associated with the Speed of Administration of Blood or Plasma —In my opinion there are two types of "speed" reactions one due to the sudden overload of the vascular system in patients with a diseased and weakened myocardium and the other associated with the production of a febrile reaction In regard to the first it is well known that intravenous fluids of any nature should not be given rapidly to patients with an impaired heart muscle as it may suddenly precipitate all of the manifestations of acute congestive failure Ordinarily the rate of injection should not exceed 10 cc per minute or 600 cc. per hour In some instances it should not be greater than 5 cc per minute although it is

institutions however either frozen, liquid or desiccated plasma is available for such purposes and is sometimes used instead of blood transfusion from a universal donor The universal donor however, still serves a useful purpose in some instances in which the rare (5 per cent) donors for the blood group AB are not available Also it is sometimes necessary to employ an Rh negative universal donor when the corresponding ABO group which was also Rh negative, is not available

There are some, however, who believe that the practice of employing the blood of a universal donor is not advisable (*180*) This is based largely on the experimental studies of agglutination titers of the serum of universal donors by Coca (*181*) and others (*182*) Furthermore it is believed by Hesse (*183*) that the indiscriminate use of such donors with a high titer of agglutinins may account for hemolytic reactions and in some instances for fatalities following blood transfusions He has reviewed the literature up to the year 1935 and collected 46 cases in which serious and sometimes fatal reactions occurred It is his opinion that a donor of this type in which the titer is 1 32 or higher is unsafe for use

I am in accord with the conclusions of Rosenthal and Vogel (*179*) who state our experience leads us to believe that the universal donor is both reliable and safe for citrate transfusions in emergencies either in civil practice or in time of war Nevertheless it is my present custom to employ the homologous groups for donors which is possible in most instances as occasionally the serum of a group O donor may contain isoagglutinins of such high titer as to hemolyze the recipient s red blood cells Furthermore as in any transfusion the careful matching of blood is carried out with respect to the determination of the effect of the recipient s serum on the donor s cells and the latter s serum on the recipient s cells

It should be concluded that although usually a universal donor can be used with safety as statistical evidence has shown nevertheless the procedure is not entirely devoid of danger as demonstrated by the following reports (*184 185 186*) In the instance reported by Weintraub the reaction was due to the high titer of the donor s isoagglutinins which caused a hemolysis of the recipient s red blood cells It has been suggested (*187*) that such a reaction can be avoided by the addition of a solution of purified A and B substance to the citrated blood of group donors to neutralize the isoagglutinins A and B which are present More recently it has been reported by Klendshoj and Witebsky (*188*) that O blood conditioned by the addition of blood group specific substances A and B has no untoward effects which can be attributed to these substances

In the case of Weintraub (*186*) 500 cc of type O, Rh negative blood was given to a patient whose blood was type A Rh positive The transfusion was followed immediately by a chill with a rise in body temperature

There is no treatment for such a reaction except an attempt at symptomatic relief from the symptoms. The remedy is prevention which in almost all instances can be accomplished by the institution of simple but rigid precautionary measures such as outlined in the article by Strumia and his associates to which reference has been made previously.

In a recent bacteriologic study of the blood in our own blood bank of the University of Michigan Hospital by Braude, Sanford, Bartlett and Mallery (*194*) bacterial contaminants were found in 2.24 per cent of 1697 pints of refrigerated blood. The organisms most frequently isolated were nonpathogenic staphylococci. Heavy growths of diphtheroids, however, produced the only febrile reaction among recipients of these contaminated blood. The patient experiencing this reaction suffered no observable harm.

More recently one of our patients who received blood from the bank went into profound shock after 45 cc. of preserved blood was injected intravenously and almost succumbed. Culture from the remaining blood in this particular container showed growths of coliform organisms of the intermediate types and E. Freundii. Blood culture from the patient was positive with a growth of coliform organism of the intermediate type. After heroic therapy with antibiotics and treatment for shock for about two days the patient made a recovery but a fatal outcome seemed imminent for at least 24 to 36 hours after the blood was injected. The details concerning this case will be reported by A. I. Braude. A severe reaction of this type has also been observed by Borden and Hall (*195*) which terminated fatally in two patients. Death in their cases was preceded by a shock syndrome accompanied by chills, fever, vomiting, diarrhea and cyanosis. In each case the condition followed the transfusion of blood which was grossly contaminated with large numbers of Achromobacter species in the first case and *Paracolobactrum aerogenoides* in the second. It is important to note that the organisms were capable of growing at low temperatures in preserved blood and did not produce macroscopic hemolysis. It was thought in these cases that the vascular collapse resulted from the injurious effects of the bacterial pyrogens on the peripheral vascular bed.

Reaction of an Allergic Nature.—Reactions on the basis of allergy occur in about 1 per cent of the recipients following blood transfusions. They are usually in the nature of a mild urticaria but in some instances more severe allergic manifestations such as true attacks of bronchial asthma, angioneurotic edema, or outspoken anaphylactic shock have been reported.

Theoretically there could be several explanations for such phenomena. Conceivably it might be that the donor is suffering from urticaria at the time the blood was withdrawn, although I have never been aware that this has occurred in my experience. Another possibility which is the one

possible in some severe cases of shock in which death seems to be impending to give 500 cc of blood or plasma in 10 minutes

In addition to the possibility of overloading the heart I am convinced that the rapid administration of blood or plasma may be followed by a febrile reaction This may be explained on the following basis if pyrogens are present in relatively weak concentrations a febrile reaction will not result when the rate of administration of the fluid in which they are present is given slowly On the other hand, the same concentration of pyrogens may be responsible for a reaction if the fluid is given at a more rapid rate As previously stated in my early experience before much was known about pyrogens our rate of febrile reactions following blood transfusion was unbelievably high In the same institution, however, the rate of reactions following the injection of the organic arsenicals for the treatment of syphilis was low The same distilled water was used for both purposes and the glassware and tubing was cared for by identical methods There was one important difference between the methods of giving the two therapeutic agents namely our blood transfusions were all administered rapidly from a container from which the flow was augmented by air pressure the antisyphilitic medication was permitted to flow in more slowly by gravity I am convinced that the difference in the rate of administration accounted for the difference in the number of reactions

Pyrogenic Reactions —It is estimated that contamination with bacteria and the products resulting from the disintegration of bacterial bodies accounts for 2 to 5 per cent of the reactions when whole citrated blood is given intravenously Since the initial work of Seibert (193), bacterial contamination has been recognized as one of the most common causes of febrile episodes following intravenous injections with either crystalline solutions with whole blood or with plasma With the proper attention to the elimination of pyrogens one very common and annoying source of reactions following blood transfusions can be eliminated or reduced to a point where they are of slight concern only The reader is referred to the paper of Strumia McGraw and Blake (53) for a practical discussion of how such reactions may be averted by the proper preparation of distilled water and cleansing of all rubber tubing and glassware

The nature of the reaction is fairly constant It usually manifests itself within 15 to 30 minutes after the intravenous injection has been given with a chill and temperature rise although sometimes the chill may be absent or exceedingly mild Associated with the febrile rise there is often a sense of malaise and sometimes nausea The reaction usually subsides within a few hours and is rarely present longer than eight hours In no instance have I seen a fatal result from such a reaction although I have observed symptoms so severe and debilitating as to have a very deleterious effect on the patient

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More recently one of our patients who received blood from the bank went into profound shock after 45 cc of preserved blood was injected intravenously and almost succumbed Culture from the remaining blood in this particular container showed growths of coliform organisms of the intermediate types and E Freundii Blood culture from the patient was positive with a growth of coliform organism of the intermediate type After heroic therapy with antibiotics and treatment for shock for about two days the patient made a recovery but a fatal outcome seemed imminent for at least 24 to 36 hours after the blood was injected The *details concerning this case will be reported by A I Braude* A severe reaction of this type has also been observed by Borden and Hall (*195*) which terminated fatally in two patients Death in their cases was preceded by a shock syndrome accompanied by chills fever vomiting diarrhea and cyanosis In each case the condition followed the transfusion of blood which was grossly contaminated with large numbers of Achromobacter species in the first case and *Paracolobactrum aerogenoides* in the second It is important to note that the organisms were capable of growing at low temperatures in preserved blood and did not produce macroscopic hemolysis It was thought in these cases that the vascular collapse resulted from the injurious effects of the bacterial pyrogens on the peripheral vascular bed

Reaction of an Allergic Nature —Reactions on the basis of allergy occur in about 1 per cent of the recipients following blood transfusions They are usually in the nature of a mild urticaria but in some instances more severe allergic manifestations such as true attacks of bronchial asthma angioneurotic edema or outspoken anaphylactic shock have been reported

Theoretically there could be several explanations for such phenomena Conceivably it might be that the donor is suffering from urticaria at the time the blood was withdrawn although I have never been aware that this has occurred in my experience Another possibility which is the one

possible in some severe cases of shock in which death seems to be impending to give 500 cc of blood or plasma in 10 minutes

In addition to the possibility of overloading the heart I am convinced that the rapid administration of blood or plasma may be followed by a febrile reaction This may be explained on the following basis if pyrogens are present in relatively weak concentrations a febrile reaction will not result when the rate of administration of the fluid in which they are present is given slowly On the other hand, the same concentration of pyrogens may be responsible for a reaction if the fluid is given at a more rapid rate As previously stated, in my early experience before much was known about pyrogens, our rate of febrile reactions following blood transfusion was unbelievably high In the same institution however, the rate of reactions following the injection of the organic arsenicals for the treatment of syphilis was low The same distilled water was used for both purposes and the glassware and tubing was cared for by identical methods *There was one important difference between the methods of* giving the two therapeutic agents namely our blood transfusions were all administered rapidly from a container from which the flow was augmented by air pressure the anti syphilitic medication was permitted to flow in more slowly by gravity I am convinced that the difference in the rate of administration accounted for the difference in the number of reactions

Pyrogenic Reactions —It is estimated that contamination with bacteria and the products resulting from the disintegration of bacterial bodies accounts for 2 to 5 per cent of the reactions when whole citrated blood is given intravenously Since the initial work of Seibert (*193*) bacterial contamination has been recognized as one of the most common causes of febrile episodes following intravenous injections with either crystalline solutions with whole blood or with plasma With the proper attention to the elimination of pyrogens one very common and annoying source of reactions following blood transfusions can be eliminated or reduced to a point where they are of slight concern only The reader is referred to the paper of Strumia McGraw and Blake (53) for a practical discussion of how such reactions may be averted by the proper preparation of distilled water and cleansing of all rubber tubing and glassware

The nature of the reaction is fairly constant It usually manifests itself within 15 to 30 minutes after the intravenous injection has been given with a chill and temperature rise although sometimes the chill may be absent or exceedingly mild Associated with the febrile rise there is often a sense of malaise and sometimes nausea The reaction usually subsides within a few hours and is rarely present longer than eight hours In no instance have I seen a fatal result from such a reaction although I have observed symptoms so severe and debilitating as to have a very deleterious effect on the patient

harm can result According to Neuhof and Hirshfeld (*200*) as much as 6 to 8 grams may be injected intravenously during a ten minute period without producing symptoms and larger quantities may be given over a longer period without ill effects Apparently the drug is rapidly oxidized and excreted so that a very large per cent of it is eliminated from the blood within a short time

Ross (*56*) concludes that transfusions of even large amounts of citrated blood are not likely to produce symptoms of citrate toxicity since the amount contained in 2500 cc of citrated blood (6 to 8 grams) is less than the toxic dose and furthermore a considerable amount of the citrate is metabolized during the time required to administer this volume of blood

In my own experience since 1917 of giving many citrated transfusions there has never been the slightest evidence in my opinion that citrate should be considered in the least harmful when given in amounts which are ordinarily employed in the average transfusion The possibility that large doses of sodium citrate might be injurious however must be considered

Transfusion Reaction Due to a Plasma Constituent of Whole Blood — In 1950 a transfusion reaction was described by Dameshek and Neber (*201*) which is apparently due to a factor in normal plasma The characteristics of this condition were chills fever backache and pain in the legs They were differentiated from pyrogenic allergic and hemolytic plasma reactions by their ease of repetition in the absence of pyrogens by a lack of the usual allergic manifestations and by the failure to demonstrate hemoglobinemia or hemoglobinuria The reaction has occurred in patients which acquired hemolytic anemia pernicious anemia sickle cell anemia leukemia aplastic anemia and in patients with terminal cancer

The observers believe that such reactions were due to a constituent of the blood plasma which can be removed from the red blood cells by washing with normal saline solution They described a provocative test which consists of the injecting 20 to 30 cc of fresh sterile plasma into patients with the described sensitivity If it is present a reaction will result at once or within 30 minutes after the injection It was demonstrated that stored heated or reconstituted dried plasma lacks the active component responsible for the condition

A study of the cause of this phenomenon has been made by Crosby and Stefanini (*202*) By inducing the condition in three patients with paroxysmal nocturnal hemoglobinuria they were able to observe the changes which occurred in the blood They found that at the time of the chill the blood became hypercoagulable although the platelet count the prothrombin activity and fibrinogen concentration were much reduced Thereafter intense fibrolytic activity developed in the plasma

most commonly accepted is that the donor might have eaten some article of diet to which the recipient is sensitive. It is claimed that such reactions can be avoided if the donors are required to present themselves for removal of blood after having refrained from food for four to six hours. The recommendation that the donors be in a fasting condition in order to avert the allergic reactions was made by Brem, Zeiler and Hammack in 1928 (*196*). The suggestion is made by Wiener and his associates (*197*) that such reactions could be on the basis of a passive transfer of reagins from the donor to the patient with the allergic symptoms arising as the result of the ingestion of food to which the donor is sensitive shortly after the transfusion. These same observers have made the observation that where a particular donor's blood has caused an allergic reaction on one occasion, a second transfusion from the same donor is likely to be followed by the same or more severe symptoms while the blood from another donor may be given with impunity.

Regardless of the cause of such allergic reactions they are not ordinarily a complication of serious importance, first, because they occur rarely, second, they are usually mild in nature, and third, they are almost always relieved promptly by the injection of 0 3 to 0 5 cc of a 1 to 1000 solution of epinephrin hydrochloride subcutaneously.

The Possible Toxic Effects of Sodium Citrate.—Since 1915 when sodium citrate was introduced as an anticoagulant in blood transfusions it has been generally accepted that in the doses ordinarily used it is without toxic effects and therefore not harmful. Now that citrated plasma is given in large amounts the possibility that citrate may have certain deleterious actions is more likely.

This problem has been studied by Bruneau and Graham (*198*) who found that dogs bled repeatedly and continually when given transfusions of citrated blood survived a much shorter time than the controls receiving heparinized blood. It was their conclusion that the difference was due to the toxic action of large amounts of sodium citrate. The clinical implication was a warning against the too liberal use of large amounts of citrated blood over a very short time.

The possibility of an overdose of citrate was suggested to Bruneau and Graham (*198*) as the result of the unexpected death of a patient following a thoracoplasty. This patient received 4000 cc of citrated blood in the short period of six hours. As the average amount of citrate which is now employed in this country is 0 35 gram per 100 cc of blood, this would make a total of 14 grams which the patient received in this relatively short interval of time. When the citrate method was introduced, Lewisohn (*199*) calculated that the fatal dose of the drug would be 15 grams for a man weighing 125 pounds and advised that not over 5 grams be used in any single blood transfusion. As the average transfusion of 500 cc contains only 1 75 grams of the drug it is unlikely that any particular

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